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Injurious Crash Risk and Medical Condition and Medication Use among Senior Drivers

by

Xinjie Cui

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy

Department of Psychology

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Dedication

To my father, mother, husband and son.

献给我的父亲，母亲，丈夫和儿子

Abstract

The objective of this study was to identify medical factors associated with injurious crash risk among senior drivers. A population-based case-control design was used. Senior drivers with at least one emergency room visit in 1997/98 or 1998/99 due to injuries related to motor vehicle crashes were identified as cases (n=915). A random sample of senior drivers from the study population was selected as controls (control/case ratio 10:1; total N=10,064).

Comprehensive information on driver characteristics (age, sex, residence and driver license), medical diagnosis and prescription medication use for the study sample was obtained from Alberta Government computerized administrative databases. The relationships between injurious crash risk and medical diagnoses in the two years preceding crash date and prescription medications dispensed during the 6 months prior to crash were examined using multivariate logistic regression modeling techniques.

In the following the major findings of the study are described. Use of non-tricyclic antidepressants, benzodiazepines, ophthalmic solutions, antibiotics, or topical antifungal medications was associated with an increased risk of injurious crash. Adjusted odds ratios (OR) for these medications ranged from 1.17 to 1.80. The relationship between diseases and injurious crash risk was complex and often involved interactions with comorbid conditions and medications. Diabetic drivers who also had disorders of joints/spine but were not on diuretic medications had an increased injurious crash risk (adjusted OR, 2.36). Female drivers with sleep disorders who were free from

acute pulmonary infection had a 3-time increase in injurious crash risk (adjusted OR, 2.98) compared to healthy male drivers, while the risk for male drivers with similar conditions was close to 2 and half times (adjusted OR, 2.42). The presence of ischemic heart disease was associated with an increase of crash risk only when patients were not using cardiovascular medications (adjusted OR: 1.38). Finally, intestinal diseases were associated with an increased injurious crash risk of 1.27 (adjusted OR: 1.27) and a history of injury was associated with an increased risk of 1.51 (adjusted OR, 1.51).

These and other results are discussed in the context of driving-related physical, psychomotor and cognitive changes caused by disease conditions and/or use of medications.

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Introduction

Each year, about 4,000 deaths and 250,000 injuries are attributed to traffic collisions in Canada (Transport Canada, 1996). In the United States, motor vehicle crashes are responsible for more than 40,000 deaths, 500,000 hospital admissions, 5,000,000 injuries and an estimated cost of $48.7 billion in lost productivity per year (Carr, 1997).

While elderly drivers account for a relatively small number of crashes, their crash risk per mile driven is second only to that of the youngest driver group (16 to24 year olds) (Transportation Research Board, 1988; National Research Council, 1988; Williams & Carsten, 1989). Furthermore, elderly drivers are more likely than younger drivers to sustain injuries or to die from a crash (Barr, 1991; Evans, 1988; Peek-Asa, Dean & Halbert, 1998). Among the elderly, traffic crashes are the second leading cause of injury and the leading cause of injury-related deaths (Evans, 1988). With the aging of the North American population and the resulting disproportionate increase of senior drivers, the magnitude of the problem will increase.

In today's western society driving is an important component of independent living. Removal of an elderly driver's driving privileges often leads to undesirable social and personal consequences such as decreased self-esteem, increased loneliness and unhappiness and even depression (Marottoli, et al., 1997). The term "age" in traffic safety research often implies "chronological age". It is a classification variable based on time elapsed since birth and does not reflect the underlying processes of physical and psychological changes (Hakamies-Blomqvist, 1998). "Aging" or "normal aging", on the other hand, refers to measurable physical and/or psychological functional decline accompanying advancing age, which are not attributable to disease processes (Wallace, 1997). There are vast inter-individual variability in aging with regard to the rate or

trajectory of functional decline and aspects of decline. Not all of the elderly drivers are unsafe drivers. Studies have shown that age, per se, is not a sensitive predictor of driving competence (Hakamies-Blomqvist, 1998). Driver restriction based solely on age is not a viable solution to traffic safety.

Clearly, restricting the driving privileges of *high-risk* elderly drivers would be a more desirable option. Medical examinations are currently required in many provinces and states for elderly drivers' license renewal, however, physicians are often not very well equipped to correctly identify high-risk drivers. This is partly due to inadequate information about the relationship between clinical measures and driving (Odenheimer, 1993). The newly published *Guide for Physicians - Determining Medical Fitness to Drive* (Canadian Medical Association, 2000) relies primarily upon expert opinion because "there is still comparatively little scientific evidence available". Therefore, it is important to conduct further scientific research to improve these guidelines. One part of this research would be to systematically identify factors that elevate older drivers' crash risk. These risk factors could then be used to develop appropriate guidelines and assessment tools for evaluation of driving competence as well as to develop interventions to reduce risk.

There are two major approaches in the study of potential risk factors for traffic crash and in the development of driving assessment tools. They are the medical approach that deals with diseases and medications and the psychological assessment approach that deals with neuropsychological measurements and functional deficits. In the following, these two approaches are described and relationships between the two approaches are discussed.

Medical Approach

Medical status is an important aspect in the study of risk factors of elderly driving. The prevalence of medical conditions and medication use increases with advancing age. There is little doubt that diseases and drugs contribute to the increased

crash risk among the elderly. Disease conditions that could cause visual, motor and cognitive impairments have up to now been the primary focus of research. These include neurological and mental disorders (e.g. dementia, stroke, depression) that have a direct impact on sensory/motor and cognitive abilities relevant to driving; cardiovascular, respiratory and cerebrovascular diseases that cause decreases in oxygen supply to the brain; and diseases that could cause sudden incapacitation of drivers such as hypoglycemia (low blood sugar), epilepsy and syncope (fainting) (Marottoli, 1997; Drachman & Swearer, 1993; Dubinsky, Williamson, Gray, & Glatt, 1992; Hansotia, 1993). Psychotropic and sedative medications have also been linked to increased crash risk (Ray & Thapa, 1993). Psychoactive drugs can alter cognitive functions, slow psychomotor activities and affect judgement and these changes in turn may have an impact on driving and can cause traffic crashes.

The medical approach to assessing crash risk has conceptual appeal. Medical care for the elderly is almost exclusively based on medical diagnosis (Wallace & Retchin, 1992). Disease and treatment terms are embedded in the language used and understood by medical professionals, and the medical care system is based almost entirely on the disease model (Wallace & Retchin, 1992). Also, data on diagnosis and on medication use are much more readily available than are measures of functional impairments.

However, the medical approach does not take *normal aging* into consideration. Yet, both medical problems and aging could alter functional capacity and result in driving impairment (Waller, 1992; Wallace, 1997). Diseases and medications are not grouped based on functional impairments. A disease entity or a medical diagnosis often implies the same affected organs, similar etiologies, symptoms and treatments. Similar cognitive impairments may result from different diseases and/or uses of different drugs. The same cognitive impairments regardless of their causes might well have the same impact on driving performance. Thus, it is logical to consider measurements of sensory/motor, cognitive and functional changes *directly* regardless of etiology in

predicting crash probabilities. The neuropsychological assessment approach reviewed below is such an approach that studies the relationships between direct measures of neuropsychological function and driving.

Neuropsychological Assessment Approach

Existing neuropsychological batteries and special tests designed to measure functional abilities related to driving have been studied in relation to indicators of driving performance (e.g. crash, driving simulator and road test). There are close relationships between tested neuropsychological functions and everyday life functional performance such as driving. However, the correspondence is far from perfect. Studies evaluating the utility of neuropsychological tests in driving assessment have been less fruitful than expected, and have produced mixed results. For instance, global cognitive function as measured by Mini-Mental State Exam (MMSE) was found to be related to driving performance in some studies (Logston, Terri & Larson, 1992), but not others (O'Neill, et al., 1992). Results on measures that assess visuospatial abilities and their relation to driving performance are also mixed. Some found that a test of visuospatial ability did not discriminate the impaired from non-impaired drivers (O'Neill, et al., 1992) and others found that a visual tracking test was highly correlated with on-road driving performance (Fitten, et al. 1995). Currently, there is no consensus on neuropsychological measures that consistently predict driving performance.

A few reasons might be responsible for the delay in establishing sensitive and consistent measures of neuropsychological functions that can assess driving competence adequately. (1) Some neuropsychological tests measure functions or skills that may have some relevance to driving but not *closely* and/or *directly*. For instance, language skills, memory, and the ability to operate telephone or balance a checkbook may have some relevance to driving performance, but it should not be surprising if they are not the most sensitive predictors of crash because they are not directly related to driving behavior. Some have suggested that measures representing "processing skills" such as visual tracking test and category fluency test (involving the ability to hold and monitor

information "on-line") may be more sensitive to driving performance (Duchek, Hunt, Ball, Buckles, & Morris, 1997). It is possible that any measure of cognitive decline may predict crash in one way or another, but this does not mean that the process itself has a direct link with driving, rather it may simply relate to more general state of cognitive deficits. (2) Neuropsychological assessments are not routinely conducted within the elderly driving population. The lack of data on pre-crash cognitive functions forces researchers to adopt "retrospective" research design strategies. Often, current measures of cognitive abilities are linked with individual's historical driving events. In this case, pre-existing impairments cannot be distinguished from impairments induced by the crash or developed after crash. The cognitive impairments caused by crashes or developed after crash may have no bearing on the occurrence of these crashes. (3) Traffic crashes are relatively rare and the majority of elderly drivers has crash-free records. For a study to have enough power to make statistically meaningful comparisons and to establish stable risk factor models, study sample size has to be large. Collecting data on neuropsychological measurements is costly. Studies of psychological risk factors on driving almost invariably suffer from small sample sizes and, thus, produce less reliable results. This may also account for some of the discrepancies among studies.

In summary, age and medical diagnosis alone are insufficient to identify high-risk drivers. Consistent and reliable driving assessment based on cognitive or functional measures that can predict crash risk with good certainty have yet to be established. Road tests have high face validity in assessing driving competency and have been regarded as the 'gold standard' for driving evaluation, but the high cost and potential risk associated with in-car test makes it unlikely for them to be used for screening purpose. More research evidence on all aspects of traffic crash risk factors needs to further be accumulated. At present, a realistic way to identify high-risk elderly drivers might be for physicians to use medical risk factors as warning signs and refer potential high-risk elderly drivers to driver evaluation programs. In these driver evaluation programs, a screening battery based on neuropsychological measures may be used to differentiate very good drivers and very poor drivers. Road tests then can be used to evaluate drivers

whose driving competence can not be determined by the screening test (Dobbs, 1997). With this combined approach, it is important not only to further identify cognitive functional measures that predict crash risk, but also to improve our understanding of the relationships between traffic crash and medical illnesses and drug treatment.

Background

In the following, studies researching potential risk factors of unsafe driving using the neuropsychological assessment approach and the medical approach are reviewed.

Sensory/Motor and Cognitive Impairments

Driving is a complex task that requires accurate sensory input, rapid information processing, reliable judgment and fast motor responses. Declines in visual abilities, speed of processing, motor movement and other cognitive functions that are associated with aging process contribute to the poor driving performance observed in elderly drivers.

Vision There is little doubt that vision is crucial to the operation of a motor vehicle. It is estimated that about 90% of the information required in driving is from visual input (Kline, Kline, Fozard, Kosnik, Schieber & Sekuler, 1992; Shipp & Penchansky, 1995). Therefore it is not surprising that driver-licensing regulations always require some form of visual ability assessment. With age there are anatomic as well as physiologic changes affecting visual abilities. As a result, even in the absence of ocular diseases, elderly people tend to have decreased visual acuity and contrast sensitivity, problems with perception of depth and shrinkage of the visual field (Wood & Troutbeck, 1995; Klein, 1991; Charman, 1997).

Kline et al. (1992) surveyed 397 drivers who were free from eye diseases and in an age range from 22 to 92 years. In the questionnaire the subjects were asked to rate the degree of visual difficulties in driving on a 4-point scale. The elderly drivers reported a higher degree of difficulty in seeing unexpected vehicles, displays with low illuminations and reading signs. They also tended to have problems judging vehicle

speed. These findings were attributed to age-related decline in near vision, contrast sensitivity, visual processing speed, visual search and dynamic vision. Similarly, elderly drivers who had stopped driving recently reported more visual difficulties along these visual function dimensions in carrying out daily visual tasks (Kosnik, et al., 1990). Wood and Troutbeck (1995) studied the effect of age and impaired vision on a closed-road test through simulated vision impairment such as decreased contrast sensitivity and glare sensitivity (by using frosted lens) and visual field restriction (by using patched eye glasses). While visual impairment affected driving performance for both young and old drivers, the impact was greater for the older drivers compared to younger ones. In addition, elderly drivers tended to compensate for the simulated visual impairment by slowing down rather than making more errors as often done by young drivers. In another road test study, healthy older drivers were found to drive at a slower speed, made fewer steering and eye movements and drifted across the center line more frequently than young control drivers (Perryman & Fitten, 1996).

Attention Driver inattention has been reported as one of the major causes of collisions among elderly drivers (Transportation Research Board, 1988). As indicated by Owsley & Ball (1993), the correlations between visual acuity and crash frequency, although statistically significant, are small. Visual attention is a much more sensitive predictor of driving performance (Owsley & Ball, 1993).

Owsley, Ball and associates have conducted a series of studies using the measure of Useful Field of View (UFOV) in predicting crash risk (Owsley, Ball, Sloane, Roenker & Bruni 1991; Owsley, e al., 1998; Sims, Owsley, Allman, Ball & Smoot, 1998; Owsley & Ball, 1993). UFOV is a measure of visual attention and speed of processing. Typically, subjects are asked to identify a briefly presented stimulus in the peripheral region of the visual field while carrying on a visual task in the central visual field simultaneously. The size of the UFOV may be reduced when a person has reduced visual sensitivity and deficits in selective attention and divided attention (Owsley et al., 1991; Owsley & Ball, 1993). In a recent case-control study of older drivers (55 and

older) with at least one at-fault crash in the previous 6 years, the logistic regression analysis showed that 40% or greater reduction of UFOV significantly predicted crash risk in the study sample (Sims, et al., 1998). Similarly, a prospective cohort study with a 3-year follow up on a group of 294 drivers 55 years and older found that drivers with reduction in UFOV were twice as likely to be involved in a traffic crash than other drivers after controlling for demographic variables, medical conditions and driving frequency (Owsley et al., 1998).

Elderly drivers are over-represented in intersection collisions and crashes related to merging into traffic and turns. Laboratory studies on reaction time have shown that the performance difference between young and old groups increases as the cognitive processing demand increases (Stelmach and Nahom, 1992; Marottoli and Drickamer, 1993). In driving situations of high complexity such as turning left at an intersection, recognition/response tasks become harder to complete successfully and elderly drivers' performance has been found to fall off sharply (Cooper, 1990). Increased crash and violation rates have been reported among cellular phone users especially those who were elderly (Violanti, 1997). High cognitive demand from complex driving situations may overload the older drivers' already reduced cognitive capacities resulting in further decline in sensory input, information processing and response output. Bad judgment may be made based on insufficient information or poor information and slow reaction time may cause delayed responses in braking, accelerating or steering which may lead to crash. A simulator study (Billheimer, Lave, Stein, Parseghian & Allen, 1986, cited in Cooper, 1990) has shown disproportionate driving impairments among those over 55 years of age when additional tasks were added to their driving workload. Under these demanding situations, elderly drivers required more information to make a decision and took more time to choose a response.

Hearing Hearing may be important when warnings of danger are given to inattentive drivers by others via auditory signal (e.g. honking) and in situations where cognitively compromised older drivers rely on passengers to provide directions for

signs, signals and locations. Hearing deficits are common problems among the elderly population (Colsher & Wallace, 1993). It is estimated that 23% to 30% of elderly are hearing impaired (Patterson & Feightner, 1997; McCloskey, Koepsell, Wolf & Buchner, 1994). In a case-control study of elderly drivers, the ownership of a hearing aid was associated with elevated risk of motor vehicle collision injuries (McCloskey et al., 1994).

Motor Function Age-associated slowing in speed of response, reduction of joint mobility and weakening of muscle strength may have an adverse effect on the initiation and execution of driving related movements such as steering, braking and shoulder checking (Stelmarch & Nahom, 1992; Marottoli and Drickamer, 1993). In fact, reduced joint flexibility has been reported to be associated with poor driving performance among older drivers (McPherson, Michael & Ostrow, 1988), and the reduction of head movement among old drivers was believed to have an effect on the perception of oncoming traffic (Isler, Parsonson, & Hansson, 1997).

Other Psychological Measures It is conceivable that a driver's behavioral tendency, emotional state, and personality traits play a role in traffic collisions. However, a recent attempt at predicting driving skills of elderly drivers with measures of personality traits failed to provide evidence for such a link (Strahan, Mercier, Mercier & O'Boyle, 1997). Some have suggested that stressful life events play a more important role in crash risk than personality traits. Drivers with economic, occupational, health and personal stress had a diminished capacity for self-control and vigilance, which placed them at a higher risk for traffic crash (Rios, Jimenez & Gacia 1987, as cited in Iancu, Spivak, Dannon, Wiener & Weizman, 1996). Studies have shown correlations between the probability of traffic collisions and certain psychological and social background characteristics such as delinquency during childhood, emotional immaturity and aggression; social stress, paranoid thinking and depression; impulsiveness, naivete and poor self-control (See Iancu, et al., 1996 for a review).

Multiple Functional Measures Some recent research efforts have been directed in a search for multi-domain and comprehensive functional measures to identify high-risk drivers. A community-living elderly cohort were surveyed and tested on self-reported adverse driving event involvement, demographic information, health status, medication use, mental state and physical performance (Marottoli, Cooney, Wagner, Doucette, & Tinetti, 1994). Poor design copying on the Mini-Mental State Exam (MMSE), fewer blocks walked and more foot abnormalities were found to be predictive of self-reported adverse traffic events. In a subsequent study of the same population with a wider range of functional measures, it was found that near vision acuity, limited neck rotation and poor visual attention were significantly linked with adverse driving events (Marottoli et al., 1998). These studies have attempted to make a comprehensive evaluation of multiple aspects of crash risk factors. The positive findings are consistent with the literature and are clinically relevant. However, as indicated by the authors, because of the limited statistical power related to relatively small sample size some risk factors might have been missed. Thus, larger scale studies are still needed.

In summary, slowing on reaction and decreased attention ability especially reduced visual attention seem to play an important role in the decline of driving ability among elderly. Comprehensive assessment of driving competency should consider the inclusion of measures of these aspects of neuropsychological functioning.

Medical Conditions

Dementia *Dementia*, especially Alzheimer's disease, is a highly prevalent disease among the elderly and has detrimental effects on driving abilities. A high proportion of dementia patients have traffic crashes after onset of the disease (Lucas-Blaustein, Filipp, Dungan, & Tune, 1988; Friedland el al., 1988; Hunt, Morris, Edwards, & Wilson, 1993; Dubinsky, Williamson, Gray, & Glatt, 1992; Drachman & Swearer,

1993). The estimated risk of crash for drivers with Alzheimer's disease is between 2.5 to 4.7 times that of age and sex matched controls (Friedland et al., 1988; Cooper, Tallman, Tuopkko, & Beattie, 1993; Tuokko, Tallman, Beattie, & Cooper, 1995). There is evidence that the crash risk increases with prolonged disease duration (Drachman & Swearer, 1993) and disease severity is associated with driving performance (Hunt, Morris, Edwards, & Wilson, 1993), although some studies have failed to find these relations (Trobe, Waller, Cook-Flannagan, Teshima, & Bieliauskas, 1996). Poor driving performance among dementia drivers has also been demonstrated in studies of road tests and driving simulator tests (Fox, Bowden, Bashford, & Smith, 1997; Rizzo, Reinach, McGehee, & Dawson, 1997; Rebok, Keyl, Bylsman, Blaustein, & Tune, 1994). Dementia patients tended to drive more slowly and make more errors -- especially on complex driving tasks (Fitten et al., 1995). However, a study of Michigan State records did not find any significant difference between traffic crash and violation rates of the AD patients and those of the matched controls (Trobe, Waller, Cook-Flannagan, Teshima & Bieliauskas, 1996). The driving mileage was not controlled for in this study. The possible reduction in driving mileage of AD patients may have kept their crash rate equal to that of control subjects. Several studies have confirmed that AD drivers tend to drive fewer miles, drive below speed limits, avoid rush hour and highway driving and also tend to drive in familiar neighborhoods (Lucas-Blaustein, et al., 1988; Trobe et al, 1996; Drachman and Swearer, 1993; Dubinsky at al., 1992). For instance, approximately two thirds of the AD patients drove fewer miles than previously (Drachman & Swearer, 1993), and they drove about 40% to 75% less than that of the controls (Dubinsky et al., 1992).

Neurological Disorders *Parkinson's Disease* patients were found to have an elevated crash rate per million-mile driven (Dubinsky et al., 1991). They also tend to perform more poorly on driving simulators (Hansotia & Broste, 1991) and on road tests (Heikkila, Turkka, Korpelainen, Kallanranta, & Summala, 1998). The crash rate of drivers with *epilepsy* was 1.3 to 2 times the rate of age-matched controls (Hansotia, 1993; Waller, 1965). The involvement of *syncope* in traffic crash was demonstrated in a

recent study of elderly at-fault drivers where 76% of those drivers whose crash cause was undetermined were shown to have positive syncope work-ups (Rehm & Ross, 1995).

Diabetes Although *hyperglycemia* and complications from *diabetes mellitus* such as retinal problems and problems with dexterity of extremities may impair driving, there is also evidence that *hypoglycemia* plays an important role in affecting the ability of driving among diabetic drivers. Transient hypoglycemia is caused by diabetes treatment with hypoglycemics such as insulin, which are often used in insulin-dependent diabetes mellitus (Hansotia, 1993). Hypoglycemia has been shown to slow cognitive and motor functions and impair simulator-driving performance (Cox, Gonder-Frederick, & Clarke, 1993). In a population-based case-control study of elderly drivers, injury risk was 2.6 times higher in older diabetic drivers, and moreover, those who were treated with insulin had a close to 6 times increase while increase for those who were on oral hypoglycemic agents was about 3 times (Koepsell et al., 1994). In a study with non-elderly population, no overall increase in the risk of motor vehicle collisions among diabetic drivers was found, but a strong positive association between the reported frequency of hypoglycemic attacks and traffic collision was evident (Stevens et al., 1989).

Arthritis The reduction in range of movement and the pain experienced by *arthritis* patients produce hesitancy in movements that are crucial for safe driving such as head turn, hand grip, wrist flexibility and foot for braking. Studies have shown that poor neck rotation, back pain, and arthritis affect the driving ability of these drivers (Morgan & King, 95; Roberts & Roberts, 1993; Hu, et al., 1998; Marottoli et al. 1998).

Ocular Diseases Age-related ocular diseases such as *cataracts, glaucoma*, and diabetic retinal problems are the leading causes of visual impairments. These conditions have been indicated in large-scale epidemiological studies where binocular visual field loss due to these conditions had doubled the crash risk (Klein, 1991; Johson & Keltner;

1983). A recent study showed that elderly drivers with decreased visual acuity and contrast sensitivity were having more difficulties in more demanding driving situations (McGwin, Chapman & Owsley, 2000). A history of glaucoma among male drivers was found to be associated with greater crash risk (Hu, Trumble, Foley, Eberhart, & Wallace, 1998).

Psychiatric Disorders *Psychiatric disorders* may cause motor retardation, inattention and aggression, which are likely to impair driving competence. However, studies of the effect of psychiatric disorder on driving are sparse and results are inconclusive. Waller (1965) reported that drivers with mental illness had twice as much risk of being involved in traffic crashes as controls, although a more recent analysis of 1,778 motor vehicle crashes showed no evidence for an increased crash rate among drivers with psychiatric diagnoses (Cushman, Good, & States, 1990).

Heart Diseases An early study on crash and chronic conditions reported to the driver licensing agency found that *heart disease* is associated with a high collision rate (Waller, 1965), however, a more recent study with a large population-based sample showed cardiovascular disease to have a small protective effect and no effect at all after controlling for age and driving mileage (Guilbert et al.,1998).

Studies of medical conditions and driving as reviewed above have adopted variety of research design methodology including retrospective survey questionnaires, experimental studies involving driving simulator tests or real-road tests, and epidemiological studies involving review of driving records. Each study has its own strengths and limitations. Some of the discrepancies among studies may be explained by methodological differences and shortcomings such as small sample size, and differences in patient selection and driving related functional measures. Information on driving history based on survey results is subject to recall bias, (e.g., Friedland, et. al, 1988; Drachman & Swearer, 1993; Dubinsky, et. al, 1992), especially among dementia patients. Some studies used case series from clinics or hospitals where controls were not

properly selected. For example, Dubinsky, et al (1992) study used volunteer controls and Lucas-Blaustein, et. al (1988) study did not have any controls. Different outcome measures have been used in these studies including crash (e.g., injurious; at-fault; fatal), traffic violation (e.g., stopped by police; speeding tickets), in-car driving performance and driving simulator tests. Although all of these outcome measures reflect certain aspects of driving behavior, it is not clear whether they share the same risk factors. For example, risk factors for fatal crash might very well be different from risk factor for minor bender-fender mishaps. Also, the validity of driving tests (road tests or driving simulators) in predicting real world crash risk has not yet established.

Comorbidity Few studies have attempted to examine the effect of diseases on driving while taking comorbidity into consideration. For those that have, many suffer from small sample size and other methodological limitations. In a retrospective cases-control study, Sims et al. (1998) examined 174 elderly drivers on their history of at-fault crash in previous 6 years and self-reported medical conditions, functional measures and current use of medications (urinary drug screen). It was found that a history of *falling* in the previous 2 years and *not taking beta-blocker* (along with black race and 40% reduction in UFOV) are risk factors for at-fault crashes. The investigators also looked at many other medical conditions such as arthritis, hypertension, depression and diabetes, and medications use such as benzodiazepines, antidepressants diuretics and NSAIDS, but found no evidence of associations. However, the retrospective nature of the study (linking current risk factors with previous driving history) and relative small sample size make the results inconclusive.

In another study examining multiple risk factors, Hu, et al.(1998) examined crash and its relation with driving exposure, driver characteristics, functional measurements, selected medical conditions and medication use from a longitudinal survey data. By using Poisson regression modeling techniques, it was found that having difficulty in extending arms in female elderly drivers, and glaucoma or antidepressants use or poor word-recall in male elderly drivers were associated with increased risk after adjusting

for mileage driven. However, many medical conditions and medications were found to have no relation to crash risk in this study. These included: self-perceived health status, cataracts, Parkinson's diseases, diabetes, heart attack, stroke, arthritis, osteoporosis NSAIDS, and benzodiazepines. Although this study has the strengths of having longitudinal data and risk factors were measured prior to the occurrence of traffic crash (prospective), the imputed values for substantial amount of missing data make the results less reliable. Also, statistical power of the study was not provided, it is not clear whether the null findings of so many medical risk factors are actually real.

In another cohort study (Foley, et. al, 1995), 1,862 elderly drivers were followed-up for 5 years and 245 crashes were observed. Information obtained from structured interview at the beginning of the follow-up included chronic diseases, symptoms, functional disabilities and medication use. Final Cox proportional hazards regression model contained measures on age (75 or older), sex (male), depression (high on depression score), back pain, NSAIDS use and poor memory recall. There were 20 chronic diseases examined in the study, but none of them were significantly associated with crash risk. These conditions included, for example, ocular diseases (glaucoma and cataracts), heart diseases, hypertension, diabetes and stroke. Since the driving exposure was not available in this study, as acknowledged by the authors, the estimation of risk was conservative and null findings are inconclusive. Also, although information on both prescription medication and over-the-counter medication was collected, it was only about the use of medication at the time of the interview. Obviously, drivers who later (within the following 5 years) involved in traffic crash may or may not be on the same medications at the time of crash. Thus the evidence for the association between NSAIDS and crash was rather weak and should be interpreted with caution.

Koepsell, et al., (1994) studied the relationship between selected medical conditions and injurious crash among elderly drivers with 235 cases and 448 age, sex and residence matched controls. Results from conditional logistic regression analysis controlling for mileage driven showed that diabetic drivers who were treated with

insulin are at highest risk and those with longer disease duration (5 year) are also at elevated risk. In addition, elderly drivers who were with both diabetes and coronary heart disease were at increased crash risk. Other medical conditions such as depression, asthma, history of fall, hypertension, dementia, syncope and other neurological diseases were not found to be associated with crash risk. This study was a population-based case-control study with proper adjustment for driving exposure. The finding of the effect of diabetes has provided strong evidence for the association between the disease conditions and injurious crash risk. However, the prevalence of certain other medical conditions among the controls was relatively low (under 2.5%). Given the sample size of 235 cases, the power for the study to detect the effect of these conditions may also be low (power calculation was not provided in the study). Thus, the null findings need to be interpreted with caution.

In summary, medical conditions such as dementia and diabetes have detrimental effects on driving and are associated with increased crash risk. Studies with multiple medical conditions have not provided enough evidence for definitive conclusions due to methodological limitations including small sample size and retrospective design.

Medications

Elderly patients consume a high proportion of all prescription drugs. In the U.S., 29% of all prescriptions are written to elderly patients who make up only 12% of the total population (Ray & Thapa, 1993; Ray, Fought, & Decker, 1992). With advancing age, increases in body fat, decreases in lean tissue, body water and serum albumin greatly affect the distribution of lipophilic and hydrophilic drugs in the body and their ability to bind with plasma protein. Reduced hepatic and renal functions affect drug metabolism and delay the clearance of drugs and their metabolites (Brawn & Castleden, 1990; Ray & Thapa, 1993; Ray, et al., 1992; Catterson, Preskorn, & Martin, 1997; Ames & Tuckwell, 1992). Medications with central nervous system (CNS) effects such as

benzodiazepines, sedative antihistamines and tricyclic antidepressants that cause cognitive and/or motor function impairments have been shown to have detrimental effects on driving.

Sedatives *Anxiolytic* and *hypnotic* drugs (such as *benzodiazepines*) are among the most highly prescribed drugs for seniors. The side effects of this class of drugs include drowsiness, decreased motor movement and coordination, dizziness and impaired memory, which can impair driving abilities. Studies have found that sedating drugs impair drivers' road tracking ability during highway driving (O'Hanlon, Haak, Blaauw, & Riemersma, 1982; O'Hanlon & Volkerts, 1986; Brookhuis, Volkerts, & O'Hanlon, 1990; O'Hanlon, et al., 1995), minor tranquilizers increase the relative risk of injurious and fatal crash by about 5 times (Skegg, Richards, & Doll, 1979), benzodiazepine users have higher accident-related health care utilization (Oster, Russell, Huse, Adams, & Imbimbo, 1987), and increased injurious crash risk (Oster et al., 1987; Neutel, Hirdes, Maxwell, & Patten, 1996; van Laar, van Willigenburg, & Volkerts, 1995; Hemmelgarnm, Suissa, Huang, Boivin, Pinard, 1997; Ray et al., 1992).

Antidepressants *Tricyclic antidepressants* have been reported to have an association with increases crash risk (Ray, et al., 1992; Leveille, et al., 1994). Antidepressants have also been shown to potentiate the effect of alcohol on driving performance (Linnoila & Seppala, 1985).

Antihistamines Although *sedative antihistamines* have been demonstrated to have adverse effect on psychomotor functions and driving abilities in laboratory tests, in simulated driving tasks and in open-road driving tests (see Ray & Thapa, 1993 for a review), evidence for their association to real world crash risk, especially among older driver, is limited.

Co-medication Three population-based studies have examined the effect of multiple medication use among elderly drivers and its effect on crash risk.

Ray et al. (1992) reviewed the prescription and driving records (495 crashes) of a cohort of 16,262 elderly (>65 years of age) Medicaid patients from Tennessee. Using Poisson regression analysis, four groups of psychoactive drugs (benzodiazepines, cyclic antidepressants, opioid analgesics and antihistamines) were examined while controlling for driver demographics, indirect measure of health status (emergency room visits and hospitalization) and use of nonpsychoactive drug use. Current users of *benzodiazepines* had an injurious crash rate 1.5 times higher than controls and a dose-dependent relationship was also evident. The use of a *tricyclic antidepressant* was associated with a 2.2 times increase in crash rate and the relationship was also dose-dependent. Also, concurrent use of more than one benzodiazepine or cyclic antidepressant was associated with even higher crash risk. Use of any of the four groups of psychoactive drugs was associated with a 50% increase in crash risk, but the use of antihistamines or analgesics only did not show significant association with crashes.

Hemmelgarn, Suissa, Huang, Boivin & Pinard (1997) conducted a case-control study in Quebec using health administrative databases, where benzodiazepine use of a group of 5,579 elderly drivers with injurious crashes was compared to a group of 13,256 controls. The rate ratio of motor vehicle crashes for current benzodiazepine users compared to controls was 1.28 after adjustment for age sex, chronic disease score (derived from drug use), and exposure to other drugs. This risk was found to be the highest in the first 7 days of long-half-life benzodiazepine use and remained higher than controls for continuous use of longer duration up to 1 year. In contrast, there was no evidence of increased crash risk for short-half-life benzodiazepines, or dose effects for any types of benzodiazepine exposure.

The above two studies have provided evidence for increased risk of actual injurious traffic crashes among elderly drivers after taking benzodiazepines. This risk is possibly higher with higher dosages or during initial period of exposure, especially for long-half-life benzodiazepines. However, another epidemiologic study conducted in

Seattle with similar methodologies, found no evidence for effects of benzodiazepines on elderly driving safety (Leveille, Buchner, Koepsell, McCloskey, Wolf, & Wagner, 1994). In this study, 234 elderly drivers who were involved in injurious motor vehicle crash and 447 controls who were matched for age sex and county of residence, were identified from a Seattle health maintenance organization's computerized database. Social-demographic and driving mileage information was collected through mail questionnaire. Crash risk was compared between users and non-users of psychoactive drugs including benzodiazepines, cyclic antidepressants, opioids and sedating antihistamines while controlling for socio-demographic factors, mileage driven, use of hypoglycemics and a chronic disease score based on pharmacy data. Although use of antidepressant and opioid analgesics was associated with increased risk for injurious crash, such association was not found for benzodiazepines and sedative antihistamines. Also, use of two or more drugs was associated with a 2-times increase in crash risk. The null finding on benzodiazepines seems to be contradictory to the results from Ray et al. study (1992). However, the most frequently prescribed benzodiazepine in this study was triazolam (50% for cases and 30% for controls) while in Ray et al.'s sample from Tennessee the most frequently used benzodiazepine was diazepam (38%). Triazolam has been shown in experimental studies to either have no effect on next-day performance or to improve performance among elderly insomniacs. Therefore, the discrepancies between this study and the others may be due to the high utilization of triazolam in this study sample. Further studies are needed to clarify the possible differential effects of triazolam and other benzodiazepines on elderly driving abilities.

The above reviewed studies on psychoactive drug use seem to suggest that cyclic antidepressants and benzodiazepine are associated with increased crash risk among elderly drivers. For all of these studies, individual medical conditions were not controlled for although there were proxy measures for health status (chronic disease score based on medication use; hospitalization or emergency room visit). Thus, it is not clear how much of the impairment is due to the effects or side effects of the medication and how much of it is due to the medical conditions being treated. Some believe that

unmedicated patients are poor drivers and that drug treatment can enhance concentration and judgement even to the extent of offsetting impairment due to the medication (Greenblatt & Shader, 1992). Others argue for a causal relationship between medication use and traffic collision (O'Hanlon et al., 1995). Studies aimed at examining effect of medications on driving should include measures of medical conditions or symptoms the drugs are used for.

The effects of medications on elderly patients are complicated not only by age-related changes in pharmacokinetics and pharmacodynamics, but also by drug interactions as a result of polypharmacy. Multiple medical conditions in many cases inevitably lead to multiple medications being prescribed. Although poly-medication represents the common clinical practice in the treatment of elderly patients, few studies have looked at how drug interactions affect driving competency. One study investigated the effects of the interaction between tricyclic antidepressants and benzodiazepines and found that the antidepressants greatly potentiate the detrimental effect that benzodiazepines have on driving (Ramaekers, Ansseau, Muntjewerff, Sweens, & O'Hanlon, 1997).

Rationale and Purpose

The occurrence of a traffic crash is determined by multiple factors including driving environment (e.g., vehicle, road, signs and speed) and driver situation (e.g., driving skill, attention, cognitive and motor functions). However, driver factors are by far the most important ones. It has been estimated that about 70-90% of motor vehicle collisions may be attributed to human errors (Cushman, et al., 1990; Katz et al., 1990). Elderly drivers' cognitive impairments and physical discomfort caused by medical conditions and/or medications would undoubtedly increase the risk of crash involvement as supported by the above reviewed literature. However, it is not clear how multiple conditions and medications interact to affect driving ability. Few studies have looked at the independent contribution of diseases or medications to increased crash risk by adequately controlling for other medical impairments. Since multiple diagnoses and poly-drug treatment are common among seniors, it is crucial for studies to assess joined and interactive effects of co-morbidity and co-medication.

The lack of studies on the combined effects of medical risk factors may be partly due to the fact that traffic crash is a rare event and it requires large numbers of cases and/or long follow-up time to obtain reliable measures of crash rates and reasonable statistical power to detect any meaningful differences. The use of health administrative databases and the linkage of crash records and health records have provided an alternative way to study the complex relationships of multiple risk factors related to motor vehicle crashes. Recent studies using such an approach have proven to be effective in examining crash risk factors (for example, Ray & Thapa, 1993; Cooper et al., 1993; Neutel et al., 1996; Koepsell, et al., 1994; Leveille, et al., 1994). Computerized administrative databases can provide objective and comprehensive information on medical measures that are free from recall-bias, a drawback of survey method. In addition, a large sample can be obtained at a relatively low cost.

The current study was an attempt to examine how driver characteristics, disease and drug interact to affect driving safety of the elderly by using driver licensing and health administrative data. The purpose was to identify medical factors that were associated with injurious traffic crash among older drivers using comprehensive information on medical diagnosis and prescription drug use from computerized health administrative databases.

Methodology

Study Design

A population based case-control research design was used in the current study. A case-control study involves, firstly, the identification of all cases (individuals with a positive outcome such as a crash event) from a defined study population in a specific study time period; and secondly, the selection of controls who are free from the outcome measure and who are representative of the study population. Then, rates of risk factors are compared between cases and controls to determine whether specific risk factors are associated with the occurrence of the outcome. Case-control studies differ from cohort studies in that cohort studies follow the entire study population through the study period. Data on exposure measures (risk factors) are collected for each individual until the outcome under study occurs or the end of the study period is reached. Theoretically, the current study could use a cohort study design. However, because of the large cohort of elderly drivers (222,000) the data extraction and analysis would become unmanageable. For instance, to obtain information on disease diagnosis, all subjects in the cohort had to be searched against Physician Claim Files which contained 2 to 3 million records each month. A case-control study is a reasonable alternative for cohort study. It is often viewed as an enhanced cohort study, especially when following an entire population is too costly and/or when the outcome measure is a rare event (Schlesselman, 1982). Observational studies can be classified as prospective or retrospective according to the temporal sequence of the measurement of risk factors and the measurement of outcome (Rothman & Greenland, 1998). If the measurement of risk factors precedes the measurement of outcome then the design is considered as prospective. If the measurement of outcome precedes the measurement of risk factors, then it is called a retrospective design. Under this definition the current study was prospective in that medical diagnosis and prescription medication use (risk factors) under study were those that occurred before injurious crash (outcome) (see Rothman & Greenland, 1998).

Study Population

The study population was defined as Alberta senior residents who had a valid driver license and were not residing in a long term care facility during the study period from April 1997 to March 1999.

Data Sources

In Alberta, as in other provinces of Canada, residents are insured under a universal health care insurance plan that is administered by the provincial government. Every time a patient visits a doctor, the doctor bills the health system and provides the system with information relevant to the care provided. Similarly, the Alberta Senior's Drug Plan covers 80% of prescription drug cost for senior residents 65 or over, and pharmacists bill the Plan directly. The data collected through these billing systems are assembled to form part of the Decision Support Environment (DSE) databases within the Ministry of Health in Alberta (Alberta Health, 1996). Other databases that are available through the DSE system are data on hospital admissions, emergency room visits, long term care, home care information and health care insurance plan registry. These databases are established for the purposes of administration and health surveillance. However, researchers may access relevant data from these databases for research purposes under agreed upon data access and usage contracts. For the current research project, all relevant data security measures and data accessing rules (Alberta Health and Wellness, 1999) were followed to ensure confidentiality and proper use.

Following are descriptions of specific data files used for the current study (Source: Alberta Health and Wellness, 1999).

Alberta Health Care Insurance Plan Registry ***(Registry File)***

This file is used to collect premiums and to assess eligibility of recipients for services claimed by practitioners. The data elements used in this study were: unique identifier (personal health number), names, date of birth, sex, postal codes and addresses of residence. The registration of Alberta Health Care Insurance Plan is mandatory in Alberta. Even individuals who opt out of the plan must be registered. Thus, data records are generally complete. All data elements were used to complete linkage with driver license data (described below).

Alberta Health Population Registry File ***(Population File)***

This file is derived from the *Registry File.* It contains information on unique identifier (personal health number), age/age group, sex, postal codes and health region. Also in this file, a migration flag indicates whether the person had moved into or out of the Province in a particular year and a death flag indicates whether death had occurred in that year. The data elements used in this study were the identifier, migration and death flags. Dates of moving in/out of the Province of Alberta or death during the study period were derived from this file.

Alberta Ambulatory Care Classification System ***(Emergency File)***

Emergency room visits and same day surgery that occurred in Alberta medical facilities has been reported to this system since April 1997. It contains data on unique identifier (personal health number), age, sex, service date and diagnostic information around the visit with up to 6 International Classification of Disease-9th edition-Clinical Modification (ICD-9-CM) diagnostic codes and up to 4 ICD-9-CM E-codes for injuries. ICD-9-CM E-codes are supplementary classification of external causes of injury and poisoning. They provide classification of environmental events, circumstances and conditions as the cause of injury and poisoning (ICD-9-CM, 1998). For instance, the codes record where the injury occurs and what causes it. The variables used in this study from this file were:

unique identifier, service date, all fields of diagnosis and E-codes. This file was used to identify cases.

Alberta Health Insurance Plan Payment Data ***(Physician Claims File)***

Claims paid to Alberta service providers under the Alberta Health Care Insurance Plan for services provided to Alberta registrants are recorded in this file. There are up to three fields for diagnoses (ICD-9-CM diagnostic codes). Other information contained in the file includes: unique identifier (personal health number), age, sex, service date, service location, health service codes and payment information. Variables used in this study were: identifier, service date and the three diagnostic fields. All medical diagnoses obtained 2-year prior to crash date were extracted from this file.

Alberta Blue Cross ***(Drug File)***

Alberta Blue Cross administers extended health benefits paid by Alberta Health and Wellness including senior residents 65 years of age or older. This subsidized Alberta Senior's Drug Plan pays 80% of the costs of drug that are listed on Alberta Drug Benefit List (Alberta Health, 1998). The major data elements in this file are unique identifier (personal health number), age, sex, dispense date, drug identifiers, drug classifications, drug quantity, drug cost and payment information. The variables used in this study were: identifier, drug classifications, drug identifier and dispense date. All prescription medications filled 6 month prior to crash date were extracted from this file.

Canadian Institute of Health Information (CIHI) Hospital Inpatient File ***(Hospital File)***

Alberta hospitals submit inpatient data to CIHI. CIHI returns the data file to Alberta Health and Wellness. Major data elements include: unique identifier (personal health number), age, sex, admission date, service provider information, diagnostic codes (up to 16 ICD-9-CM), procedure codes (up to 10 ICD-9-CM)

and information on patient classification systems. The variables used in this study were: identifier and admission date. Information on hospitalization during the 2-year time period before crash was derived from this file.

*Long Term Care Resident Classification File (**LTC File**)*

This file was established for the assessment of residents in facility-based long-term care. The relevant data elements used in this study were: unique identifier and admission date. Information on admission to LTC institutions was obtained from this file.

*Alberta Motor Vehicle Operator File (**Driver File**)*

This file was obtained from Alberta Registry Department of Government Services. It contains demographic and driver license information on all Alberta drivers. Relevant data elements used in this study included: names, date of birth, sex, addresses of residence, license issue date, license expiry date and driver license class. Driver license information came from this file and personal information was used in data linkage between Driver File and Registry File.

Data Linkage and Assembly

An electronic version of the Driver File was acquired from Alberta Registry Department of Government Services which is responsible for driver registration in Alberta. A data agreement was established to ensure confidentiality and proper use of the data. The health files and the Driver File did not share unique identifiers. To make the driver license information usable for the study, record linkage had to be conducted. There are two types of record linkage: deterministic linkage and probabilistic linkage. Both of these methods bring together of information from two records that are believed to relate to the same individual. In deterministic linkage, a "link" refers to exact match of records based on linkage criteria while in probabilistic linkage, "linking" involves

calculation of probabilities of match based on distribution of linking characteristics in a linked file (Newcombe, 1988).

Probabilistic linkage is usually carried out by using commercially available computer software. A proper software program was not readily available to the investigator at the time of data analysis. The deterministic linkage approach was first tried out and linkage rate was satisfactory. Thus probabilistic linkage was not further pursued.

The deterministic data linkage between the Registry File and Driver File was performed using SAS (version 6.12) software application (SAS Institute, 1989). Detailed linkage rules and matches are listed in Appendix A. The overall linkage rate for all potential cases and controls was 85%. The unlinked drivers tended to be older (mean age of linked drivers = 72.1, mean age of unlinked drivers = 72.7, $t = 20.5$ $df = 262{,}538$ $p < .0001$). There were more female drivers in the unlinked file than in the linked one (percent female in linked file = 40%, percent female in unlinked file = 47%, $\chi^2 = 968.9$ $df=1$, $p < .0001$). In order to avoid selection bias, only cases that were linked to the driver license files were included in the study sample and controls were randomly drawn from the linked driver file (see next section for details)

Other health files including Hospital, Physician Claims, Drug, LTC, population and Emergency were assembled by using the unique identifier (personal health number) shared by these databases. A graphic representation of the file linkage and sample selection is presented in Appendix B.

Sample Selection

The following criteria were considered in the selection of cases and controls:

(a) Age: The measure of medication use involved prescription medications filled within 6 months prior to the event date. Because medication data are available only for seniors 65 and older, subjects must be in the system for at least 6 months before the necessary information has accumulated. Thus, study subjects were required to be at least 65.5 years old or older on the event date.

(b) Residence: Information on medical conditions was obtained from individuals' health records within a 2-year time period immediately before the event date. In order to have complete data, subjects had to reside in Alberta continuously for at least 2 years prior to the event date.

(c) Long term care: Long term care facility residents are elders who are very unlikely to be driving. Furthermore, data on care or medication received from the facility are not readily available. Therefore, individuals who resided in long term care facilities in the 2-year time period before the event date were excluded from the study.

(d) Driver's license: Individuals had to have a valid driver license on the assigned event date.

Case Selection

Cases were defined as individuals who had had at least one emergency room visit due to motor vehicle crash related injuries in the study period. Since it is possible that individuals with a driver license can be injured as passengers, cases were required to be drivers at the time of crash as indicated by E-codes in the emergency medical records. Cases were identified from the Emergency File. All records with E-codes indicating motor-vehicle-crash-related injury as drivers were extracted (see Appendix C for details on a list of E-codes that were used to define cases in this study). Multiple visits for the same individuals were examined manually and decisions were made as to whether the visits belong to the same episode of crash injury or were separate episodes based on diagnoses and time lags between visits. The general rule was that if the visits were more than 6 months apart and the diagnoses of later visits had no apparent relation to earlier

ones, then these visits were deemed as results of different episodes. Otherwise, the same episode of crash was assumed. For instance, if an individual had three emergency room visits within one month and the diagnoses and E-codes for these three visits were similar, then the three visits were considered to be from the same episode of car crash. This individual would be entered into the study as a case only once. However, if a person had two emergency room visits that were more than 6 months apart and the diagnoses were not closely related (e.g. "broken arm" on the first visit and "concussion" on the second), then the injuries were considered as from two separate episodes of traffic crashes. This individual would be entered the study twice. In this study sample, four individuals were found to have two separate crash episodes within the two-year study period.

The date of the first emergency room visit within the same crash episode was used as a proxy for crash date for cases and is labeled as *event date*.

Control Selection

After cases were selected and removed, the study population formed a potential control subject pool. For each case, several steps were followed to select controls. First, all individuals in the control subject pool were assigned an event date corresponding to the crash date of that case. Second, all individuals in the control pool were compared against control selection criteria (see below) to determine eligibility as controls for that case. Third, ten controls for that case were randomly selected from all eligible controls and flagged. Fourth, these ten controls were put back to the control subject pool for the next case. This process was repeated for every case in the sample. As a result of this procedure, there were individuals who served as controls for more than one case (Rothman & Greenland, 1998, p. 98). However, because the same individual control would have different event date for each corresponding case, the control might have different medical and drug profiles as controls for different cases.

The following are criteria that were used for control selection. Here, "in migration" and "out migration" means moving into or out of the Province of Alberta. Potential controls for a particular case could not have any of the following:

1. Driver license expiry date < event date
2. Driver license issue date > event date
3. Long term care facility start date < event date
4. In migration date + 2 years > event date
5. Out migration date < event date
6. Death date < event date

Sample Size

Only cases that were linked to the driver license files were included in the study sample. Of the 1,107 cases identified from emergency service data, 921 were linked to the driver license file. The linkage rate (83%) was similar to the overall rate (85%). Among the 921 linked cases, 4 had lived in Alberta for less than 2 years and 2 other subjects had moved out of Alberta during the 2-year time period before crash. After removing these 6 subjects, the number of cases came down to 915. A control/case ratio of 10:1 was used and the total sample size was 11,065. The selection of control/case ratio was based on two criteria: (a) to maximize the power of the study (Schlesselman, 1982); (b) to minimize the computing burden.

Power Calculations

With 915 cases and a control/case ratio at 10:1, the power for detecting a relative risk of 1.25 for an exposure rate of 20% was approximately 80%. The same power could detect an odds ratio of 1.5 if the prevalence of a risk factor in control group was 5%. For any risk factor that had an exposure rate 1%, 80% power would detect an odds ratio of 2.0 (Schlesselman, 1982. See Appendix D for more detailed calculations).

Variable Specification

Data from the Physician Claims File and the Drug File provided information on all medical diagnoses obtained and prescription medications filled by each individual in the study. Theoretically, any individual disease and/or drug could be studied. However, most of the individual ICD-9-CM diagnoses or individual drugs had a very low prevalence among the study sample. Furthermore, with a sample size of 915 (cases), only a maximum of 90 factors could be studied effectively (Schlesselman, 1982; Hosmer & Lemeshow, 1989). Therefore, the purpose for studying the relationship between medical factors and crash risk is better served when diseases and drugs are grouped or further categorized.

The following criteria were used to group the initial variables selected:

1. Categories of medical diagnosis and prescription drugs that have been indicated in the literature to have an effect on driving were used. These include the following diseases: dementia, depression, sleep disturbances, other psychiatric disorders, alcohol/drug abuse, anxiety, epilepsy, syncope/narcolepsy, cataracts, glaucoma, hearing loss, joint/spine disorders, diabetes, heart diseases, chronic obstructive pulmonary disease (COPD), and a history of injury; and drugs: antidepressants, benzodiazepines, other sedatives, anticonvulsants, opioids, nonsteroidal anti-inflammatory drugs (NSAIDS), insulin and other hypoglycemics.

2. Included also were medical conditions and medications that may conceivably have some adverse effect on driving, even though they have not been studied in previous studies. These include problems of the bladder and urethra (including urinary incontinence), visual disturbances, malaise and migraine, other

neurological disorders, drugs for the eye and antiemetics (an anti-nausea and anti-vomiting drug).

3. Some categories that were of interest but had low frequencies in the study sample were combined with other similar categories. Alzheimer's disease was combined with other dementia; Parkinson's disease was combined with other extrapyramidal movement disorders and stroke and narcolepsy (falling into sleep suddenly) were combined with syncope and dizziness. Narcolepsy could probably be included with other sleep disorders. However, because its effect on driving more closely resembles the effect of syncope (causing sudden incapacitation) than insomnia or apnea, it was grouped with syncope.

4. Rare diseases or drug categories that could not be reasonably combined with other categories and did not have obvious clinical relevance to driving were excluded from this study. These include appendicitis, congenital anomaly, digestants, and antineoplastic agents.

5. Some highly prevalent disease categories and commonly prescribed medications, although with no obvious relevance to safe driving, were also studied. These include the following medical conditions: cancers, benign tumors, infectious diseases, and respiratory, digestive and kidney diseases; and the following drugs: digestive drugs, antibiotics, anticoagulants and antilipemics.

6. Diagnostic categories of other major systems and drug groups that did not fit in any of the above criteria were included here. These were disorders of the skin, diseases of blood formation, diseases of the genitourinary system and use of estrogen and cortical steroids.

7. An initial analysis was conducted with different disease and drug groupings. If a broad category had shown an effect and there were reasons to suspect that only

subcategories of that broad category might have the effect on crash, then the broad category were further broken down to subcategories. Diseases of the eye were initially included as a single category but later subdivided into finer categories. Antifungal agents were later broken down into antifungal antibiotics and topical antifungal agents.

8. After the initial analysis, drugs or medical conditions that had similar biological effects and similar effects in their relation to crash risk were further combined. Beta-blockers, Angiotesin Converting Enzyme (ACE) inhibitors, hypotensives and vasodilators were grouped as one category. Miotics (shrink the pupil) and mydriatics (enlarge the pupil) were combined with all other ophthalmic solutions.

9. Care was also taken to form disease and treatment pairs or groups wherever possible. These include, for instance, diabetes, insulin and other hypoglycemics as a group; antibiotics and infections of the respiratory system as a pair, and diseases and drugs for the digestive system as a pair (see Appendix F Table F2 for a detailed list of groups).

Final Study File

Outcome Measure

The outcome measure of the study was the occurrence of an injurious traffic crash as measured by an emergency room visit due to motor vehicle collision related injuries. Please refer to Appendix C for E-codes that were used in the identification of crash related injuries. The outcome variable was dichotomously coded with 1 as a positive injury outcome and 0 as free from crash injury.

Demographic Measures

Demographic factors including age, sex, and urban/rural residence were used in the analysis. Age, sex and driving environment were known to have associations with crash risk. Research has shown that urban and city center driving is more dangerous than rural driving (Lefrancois, R. & D'Amours, M., 1997) in terms of number of crashes, males tend to drive more than females (Hu, et al., 1998), and age is known to be associated with multiple medical conditions.

Age was calculated based on date of birth and date of event and it was used as a continuous variable with individual year of age as the measure. The urban and rural residence was determined by postal codes where urban represents cities and towns. Canadian postal codes consist of 6 characters and the first two characters can be used to differentiate rural and urban locations. In Alberta, if the first two characters of a postal code are "T0", then the postal code indicates a rural location (Canada Post, 2000). In the Study File, rural areas were coded as "0" and urban areas were coded as "1". Female drivers were coded as "0" and male as "1" for the "sex" variable.

Medical Measures

Disease Categories For all individuals in the study sample (cases and controls), health records in the computerized Physician Claims File were searched. All diagnoses obtained for the 2 year time period prior to event date for each subject were extracted and tallied. If an individual had at least one visit recorded in the Claims file with a diagnosis within the defined time period, the individual was considered to have been diagnosed with that disease and coded as positive in the corresponding disease category variable. Multiple diagnoses for the same visit were all extracted and all were treated as

valid diagnoses. Multiple visits for the same diagnosis were not given extra weights in determining whether one had the disease or not.

Table 1 shows the complete list of disease categories that were used in the study. There were total 46 categories. All disease variables were coded with "1" and "0" to indicate positive and negative diagnosis in each category.

Table 1 Disease Category, Variable Name and ICD-9-CM Diagnoses

Disease Category	Variable Name	ICD-9-CM Codes	Diagnoses / Diagnostic Categories
		Mental Disorders	
Depression	DEPRESS	296	Affective psychosis (major, bipolar, other)
		311	Depressive Disorder NEC
		3004	Neurotic Depression
		3091	Prolonged Depressive Reaction
Anxiety	ANXIETY	3000	Anxiety State
Alcohol/drug abuse	ALCOHOL	303-305	Alcohol/Drug Dependence/Abuse
		291-292	Alcoholic/Drug Psychosis
Other Psychiatric disorders	OTH_PSYC	295	Schizophrenic Disorders
		297	Paranoid States
		298	Other Non-organic Psychosis
		300	Neurotic Disorders (exclude 3000, 3004)
		301	Personality Disorders
Sleep Disturbances	SLEEP_DIS	7805	Sleep Disturbance
		01A*	Insomnia
		3074	Sleep Disorder of Non-Organic Origin
Malaise and Migraine	MALAISE	7807	Malaise and Fatigue

Disease Category	Variable Name	ICD-9-CM Codes	Diagnoses / Diagnostic Categories
		05E*	Lethargy
		06E*	Fatigue
		07E*	General Malaise
		346	Migraine
		7840	Headache
		30781	Tension Headache
Neurological Diseases			
Epilepsy	EPILEPSY	345	Epilepsy
Syncope/Narcolepsy	SYN-NAR	7802	Syncope and Collapse
		7804	Dizziness and Giddiness
		12E*	Syncope – unconsciousness
		13E*	Fainting - vaso-vago attack
		14E*	Dizziness – vertigo
		347	Narcolepsy
		7803	Convulsion
Dementia	DEMENTIA	290	Senile Organic Psychotic Condition
		331	Other Cerebral Degeneration
		3310	Alzheimer's Disease
		797	Senility
		2941	Dementia in Conditions Classified Elsewhere
Movement Disorders and Stroke	NEUR_MOV	332	Parkinson's Disease
		333	Other Extrapyramidal Diseases
		342,344, 348,438	Late effect of stroke
Other Cerebrovascular Diseases	OTH_CERE	430-437	Subarachnoid/intracerebral Hemorrhage
			Transient Cerebral Ischemia
			Other Cerebrovascular Diseases
Ocular Diseases			

Disease Category	Variable Name	ICD-9-CM Codes	Diagnoses / Diagnostic Categories
Cataracts	CATARACT	366	Cataracts
Glaucoma	GLAUCOMA	365	Glaucoma
Retinal Disorders	RETINAL	361	Retinal Detachment and Defects
		362	Other Retinal Disorders
Disorders of Cornea and Conjunctiva	COR_CONJ	370	Keratitis
		371	Other Disorder of Cornea
		372	Disorders of Conjuctiva
Disorders of Eyelids	EYELIDS	373	Inflammation of Eyelids
		374	Other Disorders of Eyelids
Visual Disturbance	VIS_DIS	368	Visual Disturbance
		369	Unspecified Visual Disturbance
Other Ocular Disorders	OTH_EYE	360	Disorders of Globe
		363,364	Disorders of Choriod, Iris and Ciliary Body
		367	Disorders of Reflections and Accommodation
		375-379	Other Disorders of the Eye
Disorders of the Ear			
Hearing Loss	HEARING	389	Hearing Loss
Disorders of Ear	EAR_DIS	380-388	Disorders of Ear and Mastoid Process
Musculoskeletal Disorders			
Disorders of Joint and Spine	JOINT_DIS	710-719	Arthropathies and related Disorders
		720-724	Dorsopathies
		2740	Gouty Arthropathy
Rheumatism	RHUMATI	725-729	Rhuematism (muscle tendons other soft tissues)
Disorders of Bone and cartilage	OSTEOPAT	730-739	Osteopathies, Chodropathies, and Acquired Musculoskeletal Deformities

Disease Category	Variable Name	ICD-9-CM Codes	Diagnoses / Diagnostic Categories
Disorders of the Endocrine System			
Disorder of Thyroid Gland	THYROID	240-246	Disorder of Thyroid Gland
Diabetes Mellitus	DIABETES	250	Diabetes Mellitus (both Type I and Type II)
Other Endocrine Glands and Metabolic Disorders	OTH_ENDO	251-259 270-279	Diseases of other Endocrine Glands Metabolic Disorders
Cardiovascular Diseases			
Ischemic Heart Disease	ISCHHD	410-414	Ischemic Heart Disease
Other Heart Disease	OTHHEART	393-398 415-429	Chronic Rheumatic Heart Disease Disease of the Pulmonary Circulation
Hypertension	HYPERTEN	401-405	Hypertensive Diseases
Blood vessel	BLD_VESS	440-448 449-459	Diseases of Arteries, Arterioles and Capillaries Diseases of Vein, Lymphatic and Other Vessel
Pulmonary Diseases			
Chronic Obstructive Pulmonary Disease	COPD	490-496	Chronic Obstructive Pulmonary Disease and Allied Conditions
Acute Respiratory Infections	RESP_INF	460-466	Acute Respiratory Infections
Other Respiratory Diseases	OTH_RESP	470-478 500-519	Other Diseases of the Upper Respiratory Tract Pneumoconioses and Other Lung Diseases Due to External Agents
Gastrointestinal Diseases			
Diseases of Stomach and	STOMACH	531-537	Diseases of Stomach and Duodenum

Disease Category	Variable Name	ICD-9-CM Codes	Diagnoses / Diagnostic Categories
Duodenum			
Diseases of Lower Digestive Tract	LOWGI_DIS	555-569	Non-infectious Enteritis and Colitis
Other Digestive Diseases	OTH_DIGE	530 540-553 570-579	Disease of Esophagus Appendicitis Other Diseases of Digestive System (liver gallbladder pancreas etc.)
Renal Diseases			
Disorders of Kidney	NEPHRITI	580-589 590-594	Nephritis and Nephrosis Other Diseases of Kidney
Disorders of Bladder and Urethra	BLADDER	595-596 597-599 788.3 625.6	Disorders of Bladder Disorders of Urethra Incontinence of Urine Stress Incontinence, Female
Injury and Poison			
Injury	INJURY	800-904 910-939 950-959	Fractures, Dislocation, Sprains, Internal Injuries and Open Wound. Superficial Injury, Contusion, Crushing. Injury to Nerves and Complications
Burns and Poisons	BURN_PSN	940-949 960-979 980-989	Burns Poison by Medicinal and Biological Substances Poison by Non-medicinal Sources
Diseases of other Systems			
Diseases of Skin and Subcutaneous Tissue	SKIN	680-709	Diseases of Skin and Subcutaneous Tissue
Cancer	CANCER	140-208	Malignant Neoplasm
Benign Tumor	BENIGN	210-239	Benign Neoplasm

Disease Category	Variable Name	ICD-9-CM Codes	Diagnoses / Diagnostic Categories
Infectious Diseases	INFECTIO	001-136	Infectious Diseases
Diseases of Blood Formation	BLOOD	280-289	Diseases of Blood and Blood-Forming Organs
Ill-defined Conditions and Symptoms and Signs	SYMPTOM	780-799	Symptoms, Signs and ill-defined Conditions (except Sleep Disturbance, Malaise and Fatigue)
Disorders of Genitourinary System	GENITOUR	610-611 614-629 600-608	Disorders of Breast Diseases of Female Genitourinary System Diseases of Male Genitourinary System

Note: * codes specific to Alberta Health Care Billing System (non ICD-9-CM codes)

Drug Categories Prescriptions dispensed within the 6 month time period prior to event date were obtained from Alberta Blue-Cross File (Drug File). There were two types of drug classification codes available from the Drug file. They were the Pharmaceutical Therapeutic Classification (PTC) codes and the Drug Identification Numbers (DIN) (Alberta Health and Wellness, 1998). A third classification, the Anatomical Therapeutic Classification (ATC), was derived from the DIN using a cross-reference file obtained from Health Canada (2000). All three classification systems were used in the categorization of drugs for the study. Detailed classifications are shown in Table 2.

For each individual in the study sample, all drug codes recorded in the Drug File in the defined time frame were extracted. They were grouped based on the classification details provided in Table 2. As long as an individual had at least one record of a study drug, the individual was considered to have used the drug before the event date and coded as positive ("1") under the corresponding drug category variable. Multiple refills of the same medication were not given more weight in determining whether one used the medication or not. All drug category variables were dichotomous variables with "1" indicating use and "0" indicating non-use of a particular drug.

Table 2 Drug Categories, Variable Name and Pharmaceutical Therapeutic Classification (PTC) Codes

Drug Categories	Variable Name	PTC Codes	Drug Class
Tricyclic Antidepressants	TRICYCLIC	281604*	Tricyclic Antidepressants
Other Antidepressants	ANTIDEPR	281604*	Other Antidepressants
Benzodiazepines	BENZODIA	282408	Benzodiazepines
Other Sedatives	OTH_SEDA	282404 282492	Barbiturates Misc Anxiolytic Sedatives and Hypnotics
Anticonvulsants	ANTICONV	281208	Benzodiazepines

Drug Categories	Variable Name	PTC Codes	Drug Class
		281212	Barbiturates
		281212*	Hydantoins
		281204	Misc Anticonvulsants
Antiparkinsonian Agents	ANTIPARK	120804	Antiparkinsonian Agents
		289200	Sumatriptan
		920000*	Levodopa and Decarboxylase Inhibitor
Opioids	OPIOIDS	280808	Opiate Agonist
		280812*	Opiate Partial Agonist
		480800*	Antitussives (Codeine, Opium Derivatives)
NSAIDS	NSAIDS	280804	Non-Steroidal Anti-inflammatory Agents
Insulin	INSULIN	682008	Insulin
Other Hypoglycemics	HYPOGLYC	682020	Sulfonylurea
		682092*	Acarbose
Estrogens	ESTROGEN	681600	Estrogens
Cortical Steroids	ADRENALS	680400	Adrenals
Antibiotics	ANTIBIO	081202	Aminoglycosides
		081206	Cephalosporins
		081207	B-Lactam
		081208	Chloramphenicol
		081212	Macrolides
		081216	Penicillins
		081224	Tetracyclines
		081228	Misc Antibiotcs
		082200	Quinolones
		082400	Sulfonamides
Antifungal	ANTIFUNG	081204	Antifungal Antibiotics
Topical Antifungal	TOPANTIF	840408**	Antifungals

Drug Categories	Variable Name	PTC Codes	Drug Class
Cardiac and hypotensives	CARVASDRG	240400	Cardiac Drugs (Beta-blocker, ACE Inhibitors)
		240800	Hypotensives
		241200	Vasodilators
Antilipemic	ANTILIPE	240600	Antilipemic Agents
Diuretics	DIURETIC	402800	Diuretics
		402810	Potassium-Sparing Diuretics
Other Electrolytic	OTH_ELEC	401000	Ammonia detoxicants
		401200	Replacement Preparation
		401800	Potassium Removing Resins
Drugs for Eye	EYE_DRG	522000	Miotics
		522400	Mydriatics
		5200**	Eye, Ear, Nose and Throat Preperations
Nose Drug	NOSE_DRG	5200**	Eye, Ear, Nose and Throat Preparations
Antiemetics	ANTIEMET	562200	Antiemetics
Digestive Drugs	GI_DRG	564000	Gastrointestinal Drugs
Anticoagulants	ANTICOAG	201204	Anticoagulants

Note: * ATC (Anatomical Therapeutic Classification) codes are used to identify the specified drugs.

**DIN (Drug Identification Number) codes are used to identify the specified drugs.

General Health Measures Individuals' general health status was designed to measure "how ill a person is". It was approximated by measures of multiple medical diagnosis, multiple drug use, and hospitalizations. There are different ways to approximate this aspect of an individual's health. For instance, numbers of diagnoses or medications given can be summed. However, this approach would give more weight to diseases that are more likely to be misdiagnosed (such as mental disorders) or to drug that are more likely to be used in conjunction with other drugs (such as drugs that require co-

medications to off set its side effects). The specific measures used in this study were the number of ICD-9-CM chapters one had obtained diagnoses in, number of classes of drugs one had been prescribed drugs for, and whether an individual was hospitalized or not in the two-year period prior to event date. An individual who had been recently hospitalized was considered to have more severe health problems and the hospitalization partly reflects a person's general state of health. Records of hospitalizations for the study sample during the 2-year period before event date were obtained from the Hospital File.

All three variables were coded as dichotomous variables. Four or more ICD-9-CM chapters were coded as "1" and three or less were cased as "0" for multiple medical conditions variable (variable name "NUM_CHP"). For the multi-drug use variable (variable name "NUM_DRG"), three or more categories of drug taken by one individual were coded as "1" and two or less were coded as "0". A code "1" in the hospitalization variable indicates that an individual had at least one hospital admission in the previous 2 years and "0" means no hospitalization occurred to that individual in the last two years.

A complete variable index is provided in Appendix E.

Analyses and Results

Driver Characteristics

There was no difference in mean age and percent of urban residence between cases and controls, although there were proportionally more men in the case group than in the control group (see Table 3).

Table 3 Descriptive Statistics

Dependent Variables	Cases	Controls	Comparisons	
Sample size N	915	9150		
Age (mean/SD)	73.1/6.0	72.8/5.8	t=1.65 df=10,063	p=.099
Age (min. – Max.)	65 – 101	65 – 93		
Sex (percent male)	63.1%	57.4%	$\chi 2$=10.9 df=1	p=.001
Urban/rural residence (percent urban)	86.1	87.3	$\chi 2$=1.1 df=1	p=.3

Descriptive Statistics of Medical Conditions and Prescription Drugs

All cases and the vast majority of controls (99.9%) had at least one diagnosis during the two-year time period before the event date. Only 14 controls had no contact with the health system within this time frame. The mean age of these 14 controls was 68 (SD 1.8) ranging from 65 to 70, while the rest of the controls had a mean age of 72.8 and a range from 65 to 93.

About 19% (177/915) of the cases did not have any prescriptions within the immediate 6-month prior to crash, while the rate was 24% (2195/9150) among controls. On average, individuals with any prescription drug use tended to be older than those who did not have any prescriptions filled before event date (mean age for non-users = 71.9 (SD=5.5), mean age for users = 73.0 (SD=5.9), $t = 7.6$ $df = 10{,}063$, $p < 0001$).

The prevalence of medical conditions and prescription drugs among cases and controls and rate ratios are listed in Table 4 and Table 5. In general, most disease categories were more prevalent in the case group than that in the control group and cases were more likely to use prescription drugs than controls.

Table 4 Prevalence of Medical Conditions and Relative Risk among Cases and Controls

Medical Condition Category	Variable Names	Rate for Cases (n=915)	Rate for Controls (n=9150)	Rate Ratio
Depression	DEPRESS	14.8	9.6	1.54
Anxiety	ANXIETY	9.2	7.6	1.21
Alcohol/drug abuse	ALCOHOL	1.4	0.9	1.56

Medical Condition Category	Variable Names	Rate for Cases (n=915)	Rate for Controls (n=9150)	Rate Ratio
Other Psychiatric disorders	OTH_PSYC	8.3	6.2	1.34
Sleep Disturbances	SLEEP_DIS	6.3	3.5	1.80
Malaise and Migraine	MALAISE	9.5	7.7	1.23
Epilepsy	EPILEPSY	1.1	0.5	2.20
Syncope/Narcolepsy	SYN_NARC	7.5	6.3	1.19
Dementia	DEMENTIA	1.4	1.6	0.88
Movement Disorders and Stroke	NEUR_MOV	1.7	1.5	1.13
Other Cerebrovascular Diseases	OTH_CERE	4.5	4.3	1.05
Cataracts	CATARACT	24.2	21.6	1.12
Glaucoma	GLAUCOMA	7.8	8.6	0.91
Retinal Disorders	RETINAL	11.1	9.1	1.22
Disorders of Cornea and Conjunctiva	COR_CONJ	14.6	10.9	1.34
Disorders of Eyelids	EYELIDS	8.3	6.8	1.22
Visual Disturbance	VIS_DIS	4.6	4.0	1.15
Other Ocular Disorders	OTH_EYE	8.4	8.2	1.02
Hearing Loss	HEARING	6.2	4.1	1.51
Disorders of Ear	EAR_DIS	18.6	17.0	1.09
Disorders of Joint and Spine	JION_DIS	50.2	40.3	1.25
Rheumatism	RHEUMATI	30.7	25.9	1.19
Disorders of Bone and cartilage	OSTEOPAT	9.8	9.5	1.03
Disorder of Thyroid Gland	THYROID	6.2	6.1	1.02
Diabetes Mellitus	DIABETES	13.9	10.2	1.36
Other Endocrine Glands and Metabolic Disorders	OTH_ENDO	17.8	17.7	1.01
Ischemic Heart Disease	ISCHHD	18.0	15.2	1.18
Other Heart Disease	OTHHEART	19.7	17.0	1.16
Hypertension	HYPERTEN	37.8	38.2	0.99
Blood vessel	BLD-VESS	13.2	11.8	1.12

Medical Condition Category	Variable Names	Rate for Cases (n=915)	Rate for Controls (n=9150)	Rate Ratio
COPD	COPD	19.0	14.7	1.29
Acute Respiratory Infections	RESP_INF	47.9	37.1	1.29
Other Respiratory Diseases	OTH_RESP	11.3	8.7	1.30
Diseases of Stomach and Duodenum	STOMACH	15.0	10.3	1.46
Diseases of Lower Digestive Tract	LOWGI_DIS	16.7	11.0	1.52
Other Digestive Diseases	OTH_DIGE	14.5	11.2	1.29
Disorders of Kidney	NEPHRITI	3.2	3.2	1.00
Disorders of Bladder and Urethra	BLADDER	15.3	13.2	1.16
Injury	INJURY	49.7	36.0	1.38
Burns and Poisons	BURN_PSN	2.4	1.3	1.85
Diseases of Skin and Subcutaneous Tissue	SKIN	43.8	36.2	1.21
Cancer	CANCER	11.9	11.5	1.03
Benign Tumor	BEHIGN	15.6	14.4	1.08
Infectious Diseases	INFECTIO	16.2	13.2	1.23
Diseases of Blood Formation	BLOOD	7.9	5.1	1.55
Ill-defined Conditions and Symptoms and Signs	SYMPTOM	71.9	66.8	1.08
Disorders of Genitourinary System	GENITOUR	24.2	21.4	1.13

Table 5 Prescription Rate and Relative Risk of Medication Use among Cases and Controls

Drug Categories	Variable Name	Rate for Cases (n=915)	Rate for Controls (n=9150)	Rate Ratio
Tricyclic Antidepressants	TRICYCLIC	3.8	3.4	1.12
Other Antidepressants	ANTIDEPR	7.3	4.0	1.83

Drug Categories	Variable Name	Rate for Cases (n=915)	Rate for Controls (n=9150)	Rate Ratio
Benzodiazepines	BENZODIA	15.4	10.2	1.51
Other Sedatives	OTH_SEDA	5.5	4.8	1.15
Anticonvulsants	ANTICONV	3.3	2.1	1.57
Antiparkinsonian Agents	ANTIPARK	0.7	1.0	0.70
Opioids	OPIOIDS	14.9	11.8	1.26
NSAIDS	NSAIDS	20.7	18.0	1.15
Insulin	INSULIN	2.7	1.7	1.59
Other Hypoglycemics	HYPOGLYC	6.6	5.8	1.14
Estrogens	ESTROGEN	7.8	9.2	0.85
Cortical Steroids	ADRENALS	11.4	7.9	1.44
Antibiotics	ANTIBIO	31.6	24.1	1.31
Antifungal	ANTIFUNG	1.4	1.5	0.93
Topical Antifungal	TOPANTIF	1.6	0.8	2.00
Cardiac and hypotensives	CARVASDRG	36.8	37.7	0.98
Antilipemic	ANTILIPE	8.6	9.7	0.89
Diuretics	DIURETIC	21.0	17.8	1.18
Other Electrolytic	OTH_ELEC	4.3	3.7	1.16
Drugs for Eye	EYE_DRG	13.0	10.0	1.30
Nose Drug	NOSE_DRG	3.3	2.0	1.65
Antiemetics	ANTIEMET	1.1	1.5	0.73
Digestive Drugs	GI_DRG	21.0	15.8	1.33
Anticoagulants	ANTICOAG	5.1	4.1	1.24

Model Building and Fitting

Overview

Multivariate logistic regression (Hosmer & Lemeshow, 1989; Kleinbaum, 1996; Rothman & Greenland, 1998) was applied using the SPSS for Windows package of

computer software (Version 10.0.5, SPSS, 1998). The dependent variable (outcome variable) was injurious crash as measured by emergency room visits due to motor vehicle related injuries. The independent variables (risk factors) included demographic factors and medical factors described above.

In the analysis, the importance of variables in regression models was assessed not only using the standard statistics (e.g. Wald test and log likelihood ratio test) but also using current knowledge about the relationships between risk factors and driving from previous research. A variable was considered ***statistically significant*** when the probability of type I error reached a predefined level. In the situation of evaluation of confounders, if the inclusion/exclusion of a variable changed the beta estimates of one or more other variables by at least 10%, then a case of ***confounding*** was considered to be established. If a factor was known to have an association with increased risk from the literature and/or it made intuitive sense for it to be related to driving, then it was considered to have ***clinical/biological significance***. For example, dementia has been demonstrated to increase the risk of crash and the disease causes changes in cognitive functions that are crucial to safe driving. Thus, dementia was deemed to have clinical relevance to traffic crash. So was the condition of urinary incontinence for it may cause driver inattention and increase the chance for a crash, even though the condition had not been confirmed to have an adverse effect on driving previously.

The analysis consisted of the following steps. **First,** a full model was fitted with all independent variables (medical factors and demographic factors) identified in the Variable Specification stage. **Second,** beta estimates and Wald tests of all variables in the model were carefully examined. Variables with *neither* clinical significance *nor* statistical significance were dropped and log likelihood ratio tests were performed to ensure that the reduced model was not statistically different from the full model. When a variable was removed from the full model, its influence on other variables was also examined to exclude possible confounding. **Third,** disease and treatment pairs or groups were analyzed for potential effects of confounding. Interactions among elements within

each pair or group were also examined at this stage. **Fourth,** variables with *neither* independent contribution to the model *nor* confounding effect on other factors were dropped and influence of the removal of these variables to the remaining variables was examined. Statistically significant factors and their confounders were kept in the model. Demographic factors remained in the model at this stage regardless of statistical significance because they were known to interact with other variables. **Fifth,** interactions among all medical factors and demographic factors from stage four were examined at this step. Only interaction terms that had both clinical relevance and statistical significance were kept in the final model.

The goodness-of-fit of the final model was tested using Hosmer-Lemeshow statistics and diagnostic analysis of residuals was carried out to further assess the fit of the model (Hosmer & Lemeshow, 1989; Kleinbaum, 1996).

Stage one: full model

All medical disease categories, drug categories and demographic factors specified through the Variable Specification process were entered into the logistic regression model. The model is shown in Appendix F Table F1. There are a total of 78 variables in the full model.

To decide the parametric scale of a continuous variable in a logistic regression model, the relationship between outcome variable and the continuous variable has to be assessed. In this study, the linearity in logit assumption was checked for continuous variable 'age' and found to be sustainable (Hosmer & Lemeshow, 1989, p. 89; see Appendix G for detail).

Stage two: reduced-model I

Diseases and drug categories of neither biological nor statistically importance in relation to crash risk were removed and in the process, the following procedures were adopted: (a) Variables were removed one at a time. (b) The effect of removing each variable to the model was assessed by log likelihood ratio test between the models with and without the variable. (c) The effects of removing each variable to other remaining variables were assessed by examining the change of beta estimates and Wald tests. (d) Log likelihood ratio test was performed on the full and reduced models to assess the effect of removing these variables as a group (Hosmer & Lemeshow, 1989; Kleinbaum, 1996).

The drug and disease categories dropped at this stage were: anticoagulants, antilipemics, electrolytics (except diuretics), estrogen, drugs for the ear, disease of the ear (except hearing loss), rheumatism, osteopathies, diseases of endocrine glands (except diabetes), disorders of the blood vessels, diseases of the respiratory system (except acute infections and COPD), digestive disorders (except stomach and lower digestive tract), diseases of the urinary and genitourinary systems, diseases of blood and blood formation system, cancers and benign tumors, infectious diseases and ill-defined symptoms and signs. The log likelihood ratio test for the full and reduced model showed no significant differences between the two models ($\chi 2 = 10.5$, df = 19, p = .96).

Stage three: analysis of disease-treatment pairs/groups

Related diseases and drug treatments were paired up or grouped. For instance, ischemic heart diseases, other heart diseases, hypertension, diuretics and other cardiovascular medications formed a group; so did diabetes and its treatment insulin and other oral hypoglycemics; and epilepsy and anticonvulsants formed a disease-treatment pair (see Appendix F Table F2 for a complete list of disease-treatment groups/pairs). These pairs and groups were analyzed to assess potential confounding and interactions within the pair or group. The analyses were performed within the "reduced-model I"

(Appendix F Table F2) which means that all other variables were kept in the background when a particular pair or group was examined. Each element in a pair/group was removed individually from the model and its impact on other variables in the group was evaluated based on changes of beta estimates and statistical significance tests. Univariate logistic models were also fitted for each variable to further assess the relationships (Appendix H). Two-way interactions among all elements *within each pair/group* were tested. Only one interaction was found to be statistically significant between elements within each pair or group. This was the interaction between ischemic heart diseases and cardiovascular drugs and the details about this interaction are described under the Final Model.

In the following, results from the analyses of each disease and treatment pair or group are described.

Depression, tricyclic antidepressants and other antidepressants

Univariate regression showed that both depression and non-tricyclic antidepressants were associated with an increased crash risk. However, when they were entered in the multivariate model the effect of depression disappeared while non-tricyclic antidepressants remained. In addition, dropping the variable "depression" substantially changed the effect estimates (18% change) of the variable "non-tricyclic antidepressants" indicating that depression was a confounder for non-tricyclic antidepressants. Tricyclic antidepressants did not show any effect on crash risk in this study sample.

Sleep disturbances, anxiety, benzodiazepines, other anxiolytics and sedatives

Although benzodiazepines and sleep disturbances were correlated, they each contributed to the multivariate model independently. The effect of anxiety was small at the univariate level and totally disappeared after other elements in the group were entered the model. Other sedatives had a negative association with crash risk when the variable was in the model with sleep disturbances and benzodiazepines, and the

inclusion of this variable changed the beta estimates (14%) of variable 'sleep disturbances'. Thus, the variable 'other sedatives' was a confounder for sleep disturbances on crash.

Diseases of the eye and ophthalmic agents

Univariate analysis indicates that being on eye drops, having problems of the retina or disorders of the cornea/conjunctiva were associated with an elevated risk of crash. Visual disturbances, cataracts, glaucoma, disorders of eyelids, and other eye diseases were not associated with crash in the univariate analysis. However, when all factors in this group were entered in the multivariate model, glaucoma showed a negative association while the eye drugs had a positive one. Disease of the cornea/conjunctiva was a confounder for eye drugs (13% change of beta estimates).

Diabetes, insulin and other hypoglycemics

Both diabetes and use of insulin were associated with higher crash risk when they were examined individually in the univariate analysis. However, when they were examined simultaneously the effect of insulin disappeared. Insulin and other hypoglycemics were confounders of diabetes, although the directions of confounding for the two types of drugs were different. The inclusion of hypoglycemics enhanced the effect of diabetes (beta changed 68%), while the inclusion of insulin decreased the effect of diabetes (beta changed 12%) as they relate to crash risk.

Heart diseases, hypertension, diuretics and cardiovascular drugs

In the multivariate analysis, diuretic drugs had a positive association with crash and the inclusion of cardiovascular drugs in the model increased this effect. Ischemic heart diseases interacted with the use of cardiovascular drugs. There was no effect for hypertension and other heart diseases, although the statistical significance of crude odds ratio (from univariate model) for other heart diseases exceeded chance levels.

Psychiatric disorders and antipsychotic drugs

Psychiatric disorders (excluding depression, anxiety, alcohol and drug abuse) had a positive association with crash risk in the univariate analysis, but the effect disappeared in the multivariate model. No associations were found for antipsychotic medications with crash risk in either the univariate or the multivariate models.

Disorders of joints and spine, other musculoskeletal disorders, NSAIDS and Opioids

All four elements in this group showed a positive association with an increased crash risk in the univariate analysis. However, when they were assessed together in the multivariate model, only joint/spine disorders was significant. No confoundings or interactions among these factors were evident.

Acute infections of the respiratory system, COPD, and antiinfectives

Oral antifungal drugs showed no effect in either the univariate analysis or the multivariate analysis. Although COPD had an association with higher crash risk in the univariate analysis, when antibiotics and acute respiratory infections were included in the model, the effect of COPD no longer existed. Antibiotics and acute pulmonary infections were correlated with each other. When they were entered simultaneously, the effect of antibiotics became marginal.

Diseases of the digestive system and drug treatment

Results from the univariate analysis showed that diseases of stomach, diseases of the lower digestive tract (intestinal diseases) as well as drugs used for digestive diseases were all associated with an increased risk of injurious crash. However, when their effects were examined in the multivariate model, only the effect of intestinal diseases remained significant. No confounding or interactions among variables in this group were found.

Other diseases and medications

Epilepsy and anticonvulsants were significant predictors in the univariate analysis, but their effects were not evident in the multivariate model.

Movement disorders (including Parkinson's disease) and antiparkinsonian agents were not predictive of crash in either univariate or multivariate analyses.

Although both skin diseases and topical antifungal drugs were predictive of crash in univariate models, the effect of skin diseases disappeared in the multivariate model while the effect of topical antifungal agents remained. There was no confounding or interaction between the two elements.

Other variables in the 'reduced model-I' that did not show any association with injurious crash risk in both univariate and multivariate analyses included: dementia, malaise, alcohol/drug abuse, syncope/narcolepsy, other cerebral disorders and antiemetics. Variables that were significant in the univariate analysis but were not significant in the multivariate analysis included: hearing loss, cortical steroids (adrenals), and burn/poisoning.

Stage four: reduced-model II

Disease and drug categories that were not directly linked (statistically) to crash risk or through confounding or interactions with other factors from the multivariate analyses of Stage Two and Stage Three were removed. In this process, the following principles were applied: (a) Variables were removed one at a time. (b) A log likelihood ratio test was performed to assess the contribution of the removed variable to the model. (c). Log likelihood ratio test was performed on the reduce-model-I and the reduced-

model-II to assess the effect of removing these variables as a group (Hosmer & Lemeshow, 1989; Kleinbaum, 1996). (d) Demographic factors were kept in the model regardless of their statistical significance so that potential interactions between these factor and medical factors could be checked at the next stage.

Variables removed at this stage were: anxiety, alcohol and drug abuse/dependence, other psychiatric disorders, antipsychotic drugs, malaise and migraine, anticonvulsants, syncope/narcolepsy, dementia, Parkinson's disease/other extra-pyramidal movement disorders, antiparkinsonian agents, other cerebral diseases, antiemetics, cataracts, retinal disorders, diseases of eyelids, visual disturbances, other problems of the eye, hearing loss, rheumatism, NSAIDS, opioid analgesics, cortical steroids (adrenals), other heart diseases, hypertension, oral antifungal agents, COPD, diseases of the stomach, drugs for digestive system, bladder problems, burns/poisoning (medication overdose) and diseases of the skin. The log likelihood ratio test between the "reduced-model I" and "reduced-model II" ($\chi 2=36.4$, df=33, p= .31) showed no statistically significant difference. The reduced model II is shown in Appendix F Table F3.

The general health measures (hospitalization, number of ICD-9-CM chapters and number of drug categories) were entered at this stage and their relations to other variables in the model were examined. Although all three measures were predictive of crash risk in the univariate models, the inclusion of the three general measures did not improve the fitting of the multivariate model ($\chi^2=6.6$, df=3, p= .08) and they were not confounded with other variables in the model either. Thus, they were excluded from further analysis.

Stage five: final model

At this stage, combinations of two-way interactions of statistically significant risk factors in the "reduced-model II" were examined. The significance of contribution of each interaction was assessed by using log likelihood ratio test between models with and without the interaction term. Only interaction terms with both biological and statistical significance were included in the final model (Table 6 and Figure 1) (Hosmer & Lemeshow, 1989; Kleinbaum, 1996).

Table 6 Final Multivariate Logistic Regression Model

Variables and Interactions	Beta estimates	S.E.	Wald Test	Sig.	Adjusted OR	95.0% C.I.for OR	
						Lower	Upper
DEPRESS	0.19	0.12	2.72	0.10	1.21	0.96	1.52
ANTIDEPR	0.44	0.16	7.62	**0.01**	1.55	1.13	2.11
SLEEP_DIS	1.09	0.27	16.52	**0.00**	2.98	1.76	5.06
BENZODIA	0.22	0.11	4.08	**0.04**	1.25	1.01	1.54
OTH_SEDA	(0.20)	0.16	1.50	0.22	0.82	0.59	1.13
GLAUCOMA	(0.34)	0.14	6.02	**0.01**	0.71	0.54	0.93
COR_CONJ	0.15	0.10	2.02	0.15	1.16	0.95	1.43
EYE_DRG	0.25	0.12	4.56	**0.03**	1.28	1.02	1.61
JOIN_DIS	0.22	0.09	6.68	**0.01**	1.25	1.06	1.48
DIABETES	0.18	0.20	0.77	0.38	1.19	0.80	1.77
INSULIN	0.29	0.25	1.35	0.24	1.34	0.82	2.18
HYPOGLYC	(0.24)	0.19	1.67	0.20	0.78	0.54	1.13
ISCHHD	0.32	0.15	4.61	**0.03**	1.38	1.03	1.86
DIURETIC	0.50	0.13	14.65	**0.00**	1.64	1.27	2.12
CARVASDRG	(0.19)	0.09	4.41	**0.04**	0.83	0.70	0.99
RESP_INF	0.31	0.08	15.71	**0.00**	1.36	1.17	1.58
ANTIBIOT	0.16	0.08	3.76	**0.05**	1.17	1.00	1.37
LOWGIDIS	0.24	0.10	5.68	**0.02**	1.27	1.04	1.54
INJURY	0.41	0.07	31.74	**0.00**	1.51	1.31	1.74
TOPANTIF	0.59	0.29	4.13	**0.04**	1.80	1.02	3.19
SEX	0.37	0.08	23.22	**0.00**	1.45	1.25	1.69
DIABETES by DIURETIC	(0.64)	0.26	5.92	**0.01**	0.53	0.32	0.88

JOIN_DIS by DIABETES	0.46	0.21	4.58	**0.03**	1.58	1.04	2.40
JOIN_DIS by DIURETIC	(0.42)	0.17	5.66	**0.02**	0.66	0.47	0.93
RESP_INF by SLEEP_DIS	(0.82)	0.30	7.38	**0.01**	0.44	0.24	0.80
SEX by SLEEP_DIS	(0.58)	0.30	3.71	**0.05**	0.56	0.31	1.01
CARVASDRG by ISCHHD	(0.42)	0.20	4.72	**0.03**	0.65	0.45	0.96
Constant	(3.14)	0.09	1,201.73	-	0.04		

Note: 1. Outcome measure: Emergency-room visit due to MVC related injuries.

2. S.E.: Standard Error.

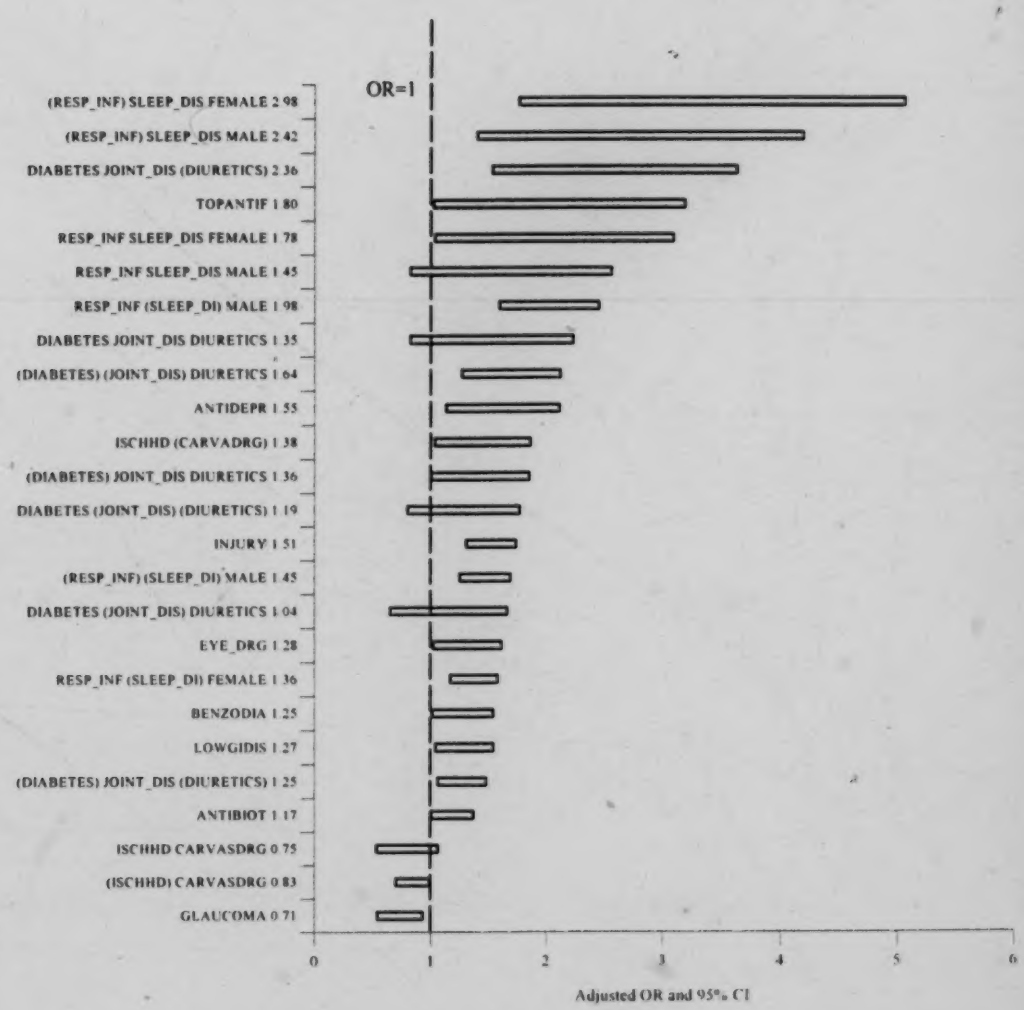
3. OR: Odds Ratio.

4. C.I.: Confidence Interval.

5. Statistical significance level in **bold** indicates $p < .05$

6. See Appendix E for a complete index on variable names.

Figure 1 Adjusted ORs and 95% CI from the Final Model



Note: 1. The Y-axis labels are variable names or combinations of variables if they are involved in interactions. Variable names in parentheses () indicate null condition on the factors. The numbers in the end are Adjusted ORs.
2. The bars on the graph show the 95% CI for Adjusted ORs.
3. See Appendix E for the complete index on variable names.
4. See Table 6 and Table 7 for detailed ORs and 95% CIs.

Simple Effects

In general, being on non-tricyclic antidepressants, benzodiazepines, antibiotics or topical antifungal agents, using eye drops or having intestinal disorders or a history of injury are associated with elevated risk for injurious traffic crash.

If a driver had a history of injury in the past two years before crash (OR 1.51; 95% CI: 1.31, 1.74) or was on non-tricyclic antidepressants (OR 1.55; 95% CI: 1.13, 2.11) in the last six months, then he/she was about 50% more likely to be in an injurious crash than those without the condition.

The risk was increased by about 25% when elderly drivers suffered from intestinal diseases (OR 1.27; 95% CI: 1.04, 1.54), were on benzodiazepines (OR 1.25; 95% CI: 1.02, 1.54) or were using ophthalmic solutions (OR 1.28; 95% CI: 1.02, 1.61). Using antibiotics was associated with 17% increase in crash risk (OR 1.17; 95% CI: 1.00, 1.37), while using topical antifungal drugs increased the risk by 80% (OR 1.80; 95% CI: 1.02, 3.19). Glaucoma had a negative association with crash risk. Having the condition of glaucoma decreased the risk by about 30% (OR 0.71; 95% CI: 0.54, 0.93).

See Figure 1 for a graphic presentation of the adjusted odds ratios from the final logistic regression model.

Interactions

The effect of diabetes, sleep disturbances, acute pulmonary infections, disorders of joints/spine, and the effect of cardiovascular drugs and diuretics depends on co-morbidity and/or co-medications. There were three groups of interactions present in the model: (1) interactions among diabetes, disorders of joints/spine, and use of diuretics; (2) interactions among sleep disturbances, history of acute respiratory infections and sex of the driver; and (3) interaction between ischemic heart disease and the use of cardiovascular drugs (see Table 7).

Diabetic drivers with a co-morbidity of joints/spine disorder were over two times more likely to be involved in an injurious crash than elderly drivers without these conditions (OR 2.36; 95% CI: 1.53, 3.63). Non-diabetic drivers with either joint problems (OR 1.64; 95% CI: 1.27, 2.12) or being on diuretic drugs (OR 1.25; 95% CI: 1.06, 1.48) or both (OR 1.36; 95% CI: 1.00, 1.85) were about 25-64% more likely to have an injurious crash. However, if a diabetic driver who had no joint problems (OR 1.04; 95% CI: 0.65, 1.66 <on diuretic>; OR 1.19; 95% CI: 0.80, 1.77 <not on diuretic>) or who had joint problems but were also on diuretic drug at the same time (OR 1.35; 95% CI: 0.82, 2.23), then his/her risk of crash was not elevated (i.e. the risk was the same as those without any of the above three conditions.).

Female drivers with sleep disorders were close to 3 times more like to be involved in a crash (OR 2.98; 95% CI: 1.76, 5.06), while the adjusted odds ratio for male drivers with sleep disorders was 2.4 (95% CI: 1.40, 4.19). The crash risk for female drivers with both pulmonary infection and sleep disturbance was 1.78 (95% CI: 1.03, 3.09), and the risk for male drivers with the same conditions was not elevated (OR 1.45, 95% CI: 0.82, 2.56). When drivers were free from sleep disturbances but suffered from respiratory infection, the odds ratio for male drivers was 1.98 (95% CI: 1.59, 2.45), but 1.36 for female drivers (95% CI: 1.17, 1.58). Male drivers who were free from these two conditions were 45% more likely to be in a traffic crash (OR 1.45; 95% CI: 1.25, 1.69) than female drivers.

Elderly drivers who were on cardiovascular drugs but with no diagnosis of ischemic heart diseases were generally less likely to be in a crash (OR 0.83, CI 0.70-0.99). On the other hand, ischemic heart disease increased crash risk by 38% when the patients were not on cardiovascular drug treatment (OR 1.38; 95% CI: 1.03, 1.86).

See Table 7 and Figure 1 for more details.

Table 7 Adjusted Odds Ratios and 95% Confidence Intervals for Factors with Interaction Terms

Variable Values			Model Parameters				
DIABETES	JOINT_DIS	DIURETICS	Beta Estimates	SE	Adjusted OR	95.0% C.I.for OR	
						Lower	Higher
1	1	1	0.30	0.26	1.35	0.82	2.23
1	0	1	0.03	0.24	1.04	0.65	1.66
1	1	0	0.86	0.22	**2.36**	1.53	3.63
1	0	0	0.18	0.20	1.19	0.80	1.77
0	1	1	0.31	0.16	**1.36**	1.00	1.85
0	0	1	0.50	0.13	**1.64**	1.27	2.12
0	1	0	0.22	0.09	**1.25**	1.06	1.48
0	0	0	Reference		1.00	1.00	1.00
RESP_INF	SLEEP_DIS	SEX					
1	1	M	0.37	0.29	1.45	0.82	2.56
1	0	M	0.68	0.11	**1.98**	1.59	2.45
0	1	M	0.88	0.28	**2.42**	1.4	4.19
0	0	M	0.37	0.08	**1.45**	1.25	1.69
1	1	F	0.58	0.28	**1.78**	1.03	3.09
1	0	F	0.31	0.08	**1.36**	1.17	1.58
0	1	F	1.09	0.27	**2.98**	1.76	5.06
0	0	F	Reference		1.00	1.00	1.00
ISCHHD	CARVASDRG						
1	1		(0.29)	0.18	0.75	0.53	1.06
1	0		0.32	0.15	**1.38**	1.03	1.86
0	1		(0.19)	0.09	**0.83**	0.70	0.99
0	0		Reference		1.00	1.00	1.00

Note: 1. "1" indicates a positive history of the specific medical condition or medication use

2. "0" indicates a negative history of the specific medical condition or medication use

3. SE: Standard Error; OR: Odds Ratio

4. **Bolded** odds ratios indicate that their 95% confidence intervals do not contain "0", thus, statistically significant.

The effect of Age, Sex and Residence

No statistically significant effects were detected for age and urban/rural residence. Sex was a strong predictor for crash and it interacted with the effect of sleep disturbances and pulmonary infections. In general, male elderly drivers were at higher risk (45% higher) than female elderly drivers when they were free from sleep disorders and acute pulmonary infections.

Assessment of Goodness-of-Fit

Hosmer-Lemeshow statistics for the final model ($\chi 2=12.0$, df=8, p=.15) showed that the final model described the data fairly well (Hosmer & Lemeshow, 1989). Hosmer-Lemeshow statistics are summary statistics that give an overall indication of the fit of the model. As noted by Hosmer and Lemeshow (1989), a fit that is indicated by these statistics do not rule out the possibility of deviations from fit for some specific data points. Thus, diagnostic tests on the residuals and leverages were also performed. The SAS software application was used in assessing diagnostics of the regression model (SAS Institute, 1995). Pearson and Deviance Residuals were used to identify observations that were not well explained by the model. CBAR was used to evaluate the influence of individual observation on parameter estimation (leverage). Results by visual examination of graphs of the diagnostics showed no significant influential or ill-fitted observations for the final model.

Discussion

In this population based case-control study, comprehensive individual health data was examined using multivariate modeling techniques. A group of medical conditions and medications were found to be associated with the risk of injurious crash among elderly drivers when comorbid conditions and co-medications were controlled for. Statistical interactions among medical factors and demographic factors were investigated and the combined effects of multiple medical conditions and medications on crash risk were noted.

The following discussion starts with a description of a few important issues that should be kept in mind when interpreting the results. Then possible explanations of the findings are provided and the strengths and limitations of the study are discussed.

Driving Exposure and Actual Risk

Driving exposure refers not only to how much one drives, but also to where, when and how often one drives. In this study, drivers' urban/rural residence measure provided some control over general driving environment (i.e. rural driving vs. city driving), however, data on how often and how far drivers drove was not available. Higher driving mileage has been found to have an association with higher crash risk (Hu, et al., 1998), although the relationship may not be linear (Hakamies-Blomqvist, 1998). It is believed that when the mileage goes up to certain extent, crash risk may actually decrease presumably due to increased experience in driving.

It is conceivable that drivers with health problems would drive less than those who are healthy. Drivers with more severe or multiple conditions may even reduce the amount of driving further. Data from previous studies suggest that this is true. Drivers

with chronic medical conditions are more likely to drive fewer miles and avoid demanding driving situations such as inclement weather, highway driving and rush hour driving, and they are also more likely to quit driving (Ball, et al, 1998; Hakamies-Blomqvist & Wahlstrom, 1998; Forrest, Bunker, Songer, Coben & Cauley, 1997; Stutts, 1998; Marottoli, et al., 1993). This reduction on driving exposure may be accomplished through self-regulation, restrictions from licensing or insurance agencies, and/or advice given by doctors, friends or family members.

Controlling for driving exposure is essential, if one is interested in the *causal relationship* between medical risk factors and traffic collision. And strictly speaking, an accurate estimation on 'causal risk' should also take the information on driving cessation due to the factors under study into consideration. However, if one's major concern is ***actual risk*** for a group of drivers with certain characteristics (e.g., drivers with certain diseases or drug use), then the estimated risk needs not to be adjusted for mileage driven. Here; actual risk is the estimated association or risk of crash for drivers with certain illnesses or drug use ***given the current practice in regulations of driving exposure***. One extreme example would be that even though blindness is a strong risk factor for motor vehicle collision, because persons who are with this condition will not obtain a driver license, their *actual risk* of crash as drivers is *zero*. We need to be cautious in interpreting null or negative results of "actual risk". Not finding an association between blindness and crash does not mean that people with the illness should start to drive. On the other hand, if the assumption that less healthy drivers drive less is believed to be true, then a positive association between a medical factor (disease or drug) and crash is likely to be real. For example, if drivers with depression are found to have higher actual risk of crash and it is reasonable to assume that these drivers drive less than their healthy counterparts, then it is likely that depression is a true risk factor for crash since it is found to increase risk even when the amount of driving is reduced. In other words, the negative correlation between illness and driving exposure biases the results towards null. Thus, any positive associations are likely to be real and, if anything, the association might be underestimated.

Information on actual risk is important in that priorities for development of interventions may be determined based on this information. With limited resources, priority might be given to target groups that are at higher *actual risk* of motor vehicle crash. For instance, based on the results from current study, in terms of prevention strategies more emphases might be given to female patient drivers with sleep disorders than, say, patients with Parkinson's disease.

Disease Severity and Confounding by Indication

Medication use represents a modifiable risk factor for crash. Thus, it is desirable to distinguish the effect of a drug and the effect of underlying medical conditions that the drug is treating. However, the relations between medication and underlying diseases are often complex. One drug could be used to treat symptoms from many different diseases and one symptom can be treated by many different drugs. Furthermore, the same disease may require different treatments at different stages of the disease process. Occasionally, there are drugs and diseases with relatively simple relations. For instance insulin is almost always used to treat insulin-dependent diabetes mellitus. Given the complexity of the relationships between drugs and medical conditions, it is not easy to disentangle the two. Any effect of a medication can be confounded by underlying diseases or disease stages (severity), unless all possible specific conditions (including severity) that are indications for the use of a medication are individually controlled for.

Confounding by indication is referred to as "an extraneous determinant of outcome parameter that is present if a perceived high risk or prognosis is an indication for intervention" (Salas, Hofman, & Stricker, 1999, p. 981). Indication (diseases or disease stage or symptoms) for use of a medication can be a confounder for the effect of the medication in that it correlates with both crash outcome and the use of the medication. One form of confounding by indication is *confounding by severity*. If a

medication is likely to be used for an advance stage of an illness and the severity of the illness is associated with crash, then the effect of the medication is confounded by the severity of the disease even when the illness itself is controlled for in the analysis.

Generally speaking, null or negative findings from this study, especially those that had been indicated in previous studies to have effects on driving should be interpreted with caution. It is likely that drivers with these conditions or indications (severity) of use of these drugs are practicing self-restrictions on driving exposure and the lack of association may be due simply to the decreases in the amount of driving.

Mental Disorders and Psychoactive Drugs

Mental disorders and psychoactive drugs can affect one's cognitive ability and cause retardation in motor functions. Drowsiness, dizziness, memory impairment and joint and muscle pain are common side effects of psychoactive drugs. Non-tricyclic antidepressants are second generation antidepressants including selective serotonin re-uptake inhibitors (SSRI) and monoamine oxidase inhibitors (MAOI). In the current study, they were found to increase the risk of injurious crash even when depression and other medical (including other mental disorders diagnoses) factors were held constant. This suggests that these antidepressants have a detrimental effect on driving that is independent of depression and other medical diseases. Although second generation antidepressant are generally believed to have less adverse side effects than tricyclic antidepressants, SSRI and MAOI could cause strong central nervous system (CNS) effects such as drowsiness, blurred vision, dizziness and insomnia (Remick, Kwan, Nirsimloo, & Schieldrop, 1994). A recent study found no differences in tests that were relevant to driving performance among hospital patients taking different types of antidepressants (Grabe, Wolf, Gratz, & Laux, 1998). In previous studies on antidepressants and driving, it was the *tricyclic* antidepressants that were found to increase crash risk (Ray & Thapa, 1993; Ray et al., 1992; Leveille, et al., 1994).

However, such a relation was not evident in this study. The lack of effect for tricyclic antidepressant here may possibly be explained by confounding by severity and a possible relation between severity and driving exposure. In other words, patients who are on tricyclic antidepressants might have more severe depressive symptoms and they may drive less.

Sleep disturbances and benzodiazepines both contribute to the increase of crash independently. Sleep disorders such as insomnia and sleep apnea could cause daytime drowsiness and are likely to affect a person's driving ability. Previous research has shown that sleep apnea is associated with increased driver injury (Connor, Whitlock, Norton, & Jackson, 2001; Teran-Santos, Jimenez-Gomez, Cordero-Guevara, Arroyo, Garcia, Quintana, et al., 1999). The strong positive relation between sleep disturbances and collision indicates that it is an influential risk factor. Moreover, female drivers' risk is even more likely to be influenced by this condition than male drivers. Benzodiazepines are strong sedatives and their relation with crash has been demonstrated repeatedly in the past (Ray, et al., 1992; Ray & Thapa, 1993; Ramaekers, et al., 1997; Hemmelgarn, et al., 1997).

Diabetes and Drug Treatment

Consistent with findings in the literature (Waller, 1965; Hansotia, 1993; Koepsell, et al., 1994), diabetes was found to increase the risk of injurious crash among elderly drivers. Moreover, there were statistical interactions between diabetes and its comorbid conditions and medication use. The combined effects of medical conditions and drugs are not always simply additive. In particular, diabetes affected driving only when the patient driver also suffered from a disease of the joints or spine. This effect was adjusted for the use of insulin, oral hypoglycemics and all other medical factors. Also of interest are the confounding effects of insulin and other hypoglycemics that pointed in different directions, namely, insulin had a positive association with crash

while other hypoglycemics had a negative one. This seems to suggest that it is the drivers with insulin-dependent diabetes mellitus who are at an undue risk. This is in line with the findings from another population-based case-control study using stratified analysis, in which diabetic drivers who were treated with insulin were at higher risk than those who were treated with oral hypoglycemics or diet alone (Koepsell, et al., 1994).

Cardiovascular Diseases and Drug Treatment

Heart diseases have long been suspected to have detrimental effects on driving. However, study results to date have been inconclusive. Waller (1965) found that heart diseases increase risk while Guibert et al. (1998) and Dionne et al. (1995) failed to find such a relation. Results from the present study suggest that whether drivers with ischemic heart diseases are at increased crash risk depend upon whether they are also on cardiovascular drugs. More specifically, it is the drivers with ischemic heart disease who *are not* on any cardiovascular medications who are at increased actual risk. In other words, there was an interaction between ischemic heart disease and cardiovascular drug use. Previous studies have not looked at interactions between heart disease and its treatment in relation to crash risk.

Diuretic drugs are often prescribed alone or in conjunction with other drugs to patients with hypertension or edema. Some diuretics could cause CNS effects which in turn could affect driving abilities (Canadian Pharmacists Association, 2000). The effect of diuretics on driving could also reflect the effect of disease conditions that are indications for the use of the medication. These conditions are likely to be less severe since diuretics are usually the first line treatment for certain cardiovascular diseases. These could be the patient drivers who are still very active and driving long distances. However, this hypothesis needs be tested in future studies. The size of the effect of diuretics on crash depends upon comorbid conditions including diabetes and disorders of

joints/spine. When drivers were on the medication but free from diabetes and joint disorders, the estimated risk is at its highest.

There is a protective effect on crash risk with the use of cardiovascular drugs including beta-blockers, ACE inhibitors, hypotensives and vasodilators. It is possible that the use of these drugs effectively controls disease symptoms and improves driving performance. This seems to be supported by a retrospective study in which *not taking beta-blockers* was found to be a risk factor even when it was adjusted for annual mileage driven (Sims, et al., 1998). However, the weakness in the design of that study (retrospective) makes the result less conclusive. It is also possible that drivers who are on cardiovascular drugs have more sever cardiovascular conditions that prohibit them from frequent driving and it is the reduced driving that protects them from high crash risk. Further studies are needed to definitely exclude this possibility.

Diseases and Drugs Affecting Sensory and Motor Abilities

Elderly drivers using ophthalmic solutions were found to have a higher risk of injurious crash after the adjustment for diseases of the cornea and conjunctiva. This finding is new. Previous studies on vision and ocular diseases have indicated that normal binocular vision and visual attention are important to safe driving and visual field loss due to eye diseases are associated with increased crash risk (Klein, 1991; Owsley, et al., 1998; Johson & Keltner; 1983). However, so far no study had looked at the effect of eye medications. It is possible that eye drops cause irritations in the eyes and contribute to a car crash. In this study, the effects of ocular diseases were accounted for by the effects of eye drugs and other medical factors. Replications of this result are needed in the future to elucidate the relationships among the use of eye drugs, underlying ocular diseases and crash.

Glaucoma has been noted in several studies for its relation to increased risk in traffic crash (Hu, et al., 1998; McGwin, Owsley & Ball, 1998; Klein, 1991). The negative relation found in the current study might be attributed to a reduction in the amount of driving by drivers with the disease.

The findings concerning problems of joints and spine are generally in line with the literature. Previous studies found back pain (Hu, et al., 1998; Foley et al., 1995), difficulty extending arms (Hu, et al., 1998) and limited neck rotation (Marottoli et al., 1998) were risk factors of car crash. The current results indicate that joint and back problems not only increase crash risk but also interact with diabetes and use of diuretics to affect driving performance. Joints/spine disorder coupled with diabetes but without diuretic drugs gives a risk close to 2 and half times of those who are free from these conditions. For drivers who suffer from joints/spine disorders and using diuretics but are without diabetes, the risk was 1.36.

Other Diseases and Medications

A history of acute respiratory infection or injury, having intestinal diseases, and being on antibiotics or topical antifungal agents are all found to be associated with elevated crash risk. Sims et al. (1998) have also associated history of injury with crash. Falls are the most common causes of injuries among the elderly population. It is possible that elderly who are "injury prone" may have cognitive impairments and/or physical frailty that predispose them to falls as well as traffic crashes. In other words, falls and crashes may share some risk factors such as cognitive impairments and lower extremity disabilities.

Among the elderly, acute respiratory infections often happen to patients who suffer from COPD. An episode of acute infection could worsen the condition of COPD. Thus, it could be either the acute infection itself (if crash occurs during the infection) or

the worsened chronic condition or both that contribute to collisions. It is generally believed that the decrease in oxygen supply to CNS due to respiratory problems causes decline in mental functions such as impaired judgment, reduced concentration, slowed response and physical weakness which in turn may affect driving ability (Marottoli, 1997; Canadian Medical Association, 2000).

The finding that antibiotics, topical antifungal drugs and intestinal diseases are risk factors for injurious crash is new to the literature. Large doses of antibiotics could cause drowsiness (Canadian Pharmacists Association, 2000). Diseases that require topical antifungal treatment such as yeast infection of skin and female genitalia can cause severe itchiness which in turn could distract driver's attention. The effect of intestinal diseases on driving could come from physical discomfort causing inattention. These findings need to be replicated in the future.

Demographic Factors

Sex is a strong predictor of injurious crash. Male drivers are more likely to be involved in a car crash than female drivers. This is likely due to higher driving exposure of the male drivers. There is evidence in the literature that sex difference may be explained by annual mileage driven (Hu, et al., 1998). No effect was found for rural/urban residence in the current study. The rural areas that were defined based on postal codes contained some small town centers. The rural/urban residence measure used might not be the most sensitive measure of rural/urban driving environment. Age was also found to have no association with crash risk. This may be due to the reduced driving associated with older age.

Medical Factors and Cognitive Impairments

Disease diagnoses are categories of pathological changes and they are grouped based on etiology, affected organs and/or symptoms and signs. The effects of diseases and medications on driving performance are likely to be mediated through cognitive, functional and/or physical impairments due to the disease processes and adverse effect of these medications. The manifestations of diseases are more directly linked to driving competency than disease diagnoses. For example, research has shown that it is the decline in visual selective attention in Alzheimer's disease that is partly responsible for the impaired driving performance in the early stages of Alzheimer's disease (Parasuraman & Nestor, 1991).

The medical factors identified in the current study to have a positive association with increased risk of injurious crash include the following diseases: sleep disorders, diseases of joints/spine, diabetes, ischemic heart diseases, acute pulmonary infections, intestinal diseases and history of injury, and following medications: antidepressants, benzodiazepines, ophthalmic solutions, diuretics, cardiovascular medications, antibiotics and topical antifungal agents. Some of them cause similar psychomotor and/or cognitive impairments. For instance, sleep disorders, antidepressants and benzodiazepines all could cause a slowing in reaction and reduced vigilance. Both pulmonary infections and heart diseases could restrict oxygen supplies to the brain causing general decline in cognitive functions including attention. The underlying diseases that a topical antifungal agent is treating and the disease of the lower digestive tract could cause similar physical discomfort and distraction.

Research has shown that attention is one of the most important cognitive factors in driving. Many of the skills involved in driving may be well automatized. However, there are times when unpredictable events occur and attentional control must be exerted. It is under such circumstances that one would expect breakdowns in driving

performance in elderly patient drivers who suffer from these medical illnesses and/or use of these medications (Duchek, et al., 1997).

Strengths

Studies with data obtained from questionnaires are subject to intentional or unintentional recall biases. Recently, McGwin et al. (1998) have shown that there are discrepancies between self-reported crashes and crashes from state records. Large computerized administrative data sources not only provide more *objective data*, but also provide more complete data, making the study of a large array of medical factors possible.

The *sample size* of the current study is one of the largest among studies of its kind. Because traffic crashes are relatively rare and the majority of drivers are crash free, it is crucial to have large sample sizes to study crash and its risk factors especially when multiple factors are considered. Large sample sizes give more power to detect associations. This advantage is reflected in the narrower range of confidence intervals of risk estimates compared to similar studies. For instance, there were 245 crashes in Foley et al. study (1995), 446 crashes in Ray et al. study (1992) and only 174 in Sims et al. study (1998). The confidence intervals of the risk estimates in these studies sometimes ranged from almost unity to up to 40 which are likely to be less accurate and less stable.

This study used a *population based case-control* design. Both cases and controls were from a geographically defined elderly driver population. This necessarily avoids referral bias that is often associated with hospital/clinic based cases-control studies (Waller, 1992).

The use of *multivariate modeling* approach to assessing the associations between medical risk factors and injurious crash risk is another strength of this study. As the results have shown, the relationships among medical factors and crash are complex. Medical factors are not only correlated, but some also interact with one another. Results

from univariate analyses do not show the complete picture and are potentially misleading. For example, medical conditions such as psychiatric disorders (except depression and anxiety), epilepsy, retinal problems, hearing loss, rheumatism, COPD, disorders of the blood formation system or GI system were all positively associated with increased crash risk with univariate analysis, but the effect disappeared in the multivariate analysis. Same relation exists for medication including anticonvulsants, NSAIDS, adrenals, GI medications and opioids analgesics. These major discrepancies between univariate models and multivariate models indicate the importance of the multivariate approach.

Limitations

One of the limitations of the study is that the statistical analysis was not based on ad-hoc hypotheses and a sequence of analyses dictated the use of results from earlier analysis to guide later analysis. This procedure has the potential to capitalize on chance relationships and therefore probabilities associated with statistical testing may be overestimates of the true relationships. Thus, the findings reported here should be regarded as tentative, and the statistical significance should only be used as guidelines for future replications.

In the study, the accuracy of medical diagnoses and compliance of medication use were not verified. Misdiagnosis and non-compliance of drug use will result in misclassifications of study factors. However, misclassifications would only lead to more conservative results because their bias is towards no association.

Information on over the counter medications was not available for this study. Of importance are uses of sedative antihistamines for allergies or cold symptoms because of the high use and high potential of sedation.

Conclusions and Future Directions

This study has confirmed some of the findings in the literature on medical risk factors and traffic crash risk among senior drivers. Because of the use of a multivariate approach and comprehensive examination on comorbidity and co-medications, the study has provided strong evidence for these findings including the associations between crash risk and diabetes, disorders of joint/spine, sleep disorders, benzodiazepines and antidepressants. This study has also provided additional information on some less intensively studied risk factors such as heart diseases, diuretics and history of injury. A few new associations were found and hypotheses may be generated from them for further investigations. These include the associations between crash risk and antibiotics, topical antifungal agents, pulmonary infections and intestinal diseases. Different combinations of diseases and/or medications were found to have different estimated risks. In addition, the risk estimates reflect actual risk of crash given current practice in regulating driver licensing and other mechanisms of self-regulation on driving exposure.

The Findings from the current study in conjunction with other findings from the literature can be used to improve guidelines for the assessment of medical fitness of driving. The identified medical risk factors can also be used as red flags for physicians to further investigate patients' situation around driving.

The relationships between medications and underlying diseases are best studied when information on severity of diseases, indications of drug use and driving exposure are examined simultaneously. Future studies are needed to verify the new findings from this study including the effect of intestinal diseases, use of topical antifungal drugs and antibiotics. The negative and null findings of this study also need to be verified in future studies. The differences shown in this study between results from univariate models and multivariate models indicate complex relationships among medical factors. Any future

study searching for medical risk factors for crash should take a multivariate approach and results from studies with univariate analysis should be interpreted with extreme caution.

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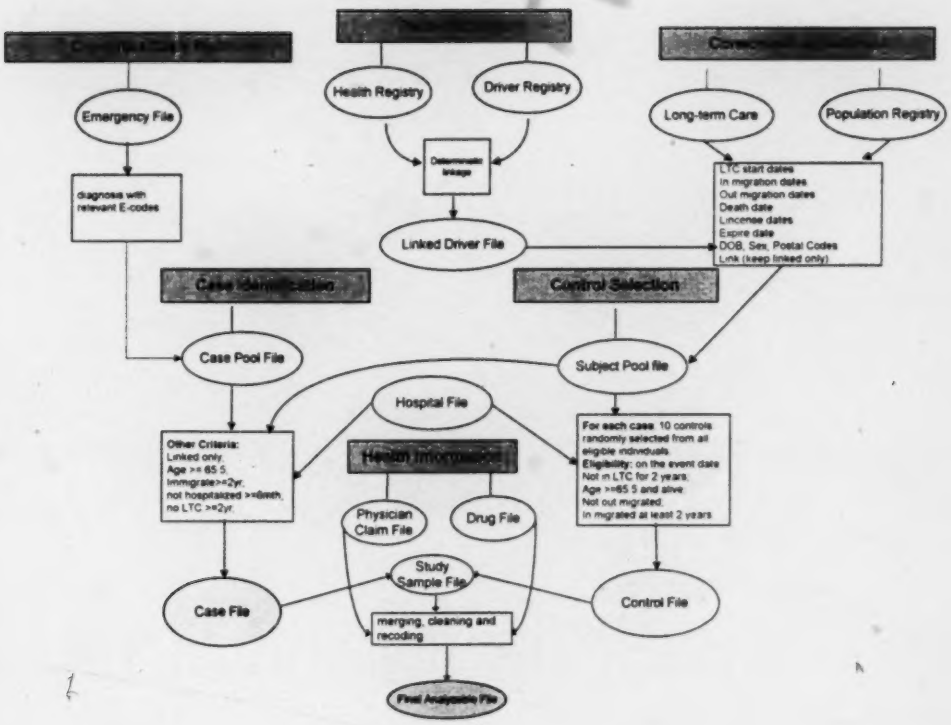
Appendix A Deterministic Linkage between Registry File and Driver File

Step	Linkage Rules							Matches	Multiple Matches	
	Surname	Middle name	First Name	Sex	DOB	PC	Address		Registry File	Driver File
1	Full	Full	Full	Yes	Yes	Yes		102,921	5	3
2	Full	Initial	Full	Yes	Yes	Yes		49,497	1	0
3	Full	Initial	Full	Yes	Yes		Partial	841	0	0
4	Full	Initial	Full	Yes	Partial	Yes		6,432	1	0
5	Full	Initial	Soundex	Yes	Partial	Yes		4,185	0	0
6	Soundex	Initial	Full	Yes	Partial	Yes		1,734	0	0
7	Full	Initial	Full		Yes	Yes		2,159	1	0
8	Full	Initial	Full	Yes	Yes			12,682	1	1
9	Soundex	Initial	Soundex	Yes	Yes	Yes		80		
10	Full	Initial	Full	Yes	Partial		Partial	46	0	0
11		Initial	Full	F	Yes	Yes		308	0	0
12	Full	1st Ini	Mid Ini	Yes	Yes	Yes		2,732	0	0
13	Initial	Initial	Full	Yes	Yes	Yes		13,815	0	0
14	Full			Yes	Yes	Yes	Partial	25,013	2	2
Total								222,445		

Note: 1. Total number of records in the driver file was 262,500 and the total linked records were 222,445. The linkage rate was 85%.

2. DOB – date of birth
3. PC – postal codes
4. Soundex: It is a build in SAS algorithm that compares names that sound alike.
5. Multiple matches are resolved by manually checking on full addresses and other information.

Appendix B Data Assembly and Linkage Chart



Appendix C ICD-9-CM E-Codes Related to Motor Vehicle Accident

International Classification of Disease 9th Revision Clinical Modification (ICD-9-CM) E-codes are supplementary classifications of external causes of injury and poisoning. They provide classification of environmental events, circumstances and conditions as the cause of injury and poisoning (ICD-9_CM, 1998).

Cases were defined as individuals who had at least *one emergency* room visit due to *injuries* related to traffic *crash* as *drivers* during the study period. Relevant E-codes under this definition are: E810 to E816, E819, E822, E823, and E825 with a 4th digit as 0. The 4th digit of "0" identifies the injured person as "driver of motor vehicle other than motorcycle". The reason for excluding other E-codes of Motor Vehicle Accidents was that the situations defined by these E-codes did not have *direct* involvement in driving. For instance, the injuries sustained by drivers while *boarding or alighting* were considers to be irrelevant to skills of driving.

Following are definitions of E-codes under "Motor Vehicle Accident" in ICD-9-CM. E-codes printed in *italic* are considered to be irrelevant to current study.

Motor Vehicle Traffic Accident (E810-E819)

E810 Motor vehicle traffic accident involving collision with train

E811 Motor vehicle traffic accident involving re-entrant collision with another motor vehicle

E812 Other motor vehicle traffic accident involving collision with motor vehicle

Includes: collision with another motor vehicle parked, stopped, stalled, disabled, or abandoned on the highway

Motor vehicle collision NOS

E813 Motor vehicle traffic accident involving collision with other vehicle

Includes: collision between motor vehicle, any kind and other road (non-motor transport) vehicle, such as: animal carrying a person, animal-drawn vehicle, pedal cycle, streetcar.

E814 Motor vehicle traffic accident involving collision with pedestrian

Includes: collision between motor vehicle, any kind, and pedestrian

Pedestrian dragged, hit, or run over by motor vehicle, any kind

E815 Other motor vehicle traffic accident involving collision on the highway

Includes: collision (due to loss of control) (on highway) between motor vehicle, any kind, and: abutment (bridge) (overpass) animal (herded) (unattended)fallen stone, traffic sign, tree, utility pole, guard rail or boundary fence, inter-highway divider, landslide (not moving), *object set by railway train or road vehicle (motor) (non-motor), object thrown in front of motor vehicle,* safety island, temporary traffic sign or marker, wall of cut made for road, other object, fixed, movable, or moving.

E816 Motor vehicle traffic accident due to loss of control, without collision on the highway

Includes: Colliding with object off the highway; overturning; stopping abruptly off the highway due to motor vehicle: failing to make curve; going out of control (due to): blowout, burst tire, driver falling asleep, driver inattention, excessive speed, failure of mechanical part.

E817 Non-collision motor vehicle traffic accident while boarding or alighting

Includes: (While boarding or alighting) Fall down stairs of motor bus, fall from car in street, injured by moving part of the vehicle, trapped by door of motor bus.

E818 Other non-collision motor vehicle traffic accident

Includes: (motor vehicle while in motion) Accidental poisoning from exhaust gas generated by; breakage of any part of; explosion of any part of; fall, jump, or being accidentally pushed from; fire starting in; hit by object thrown into or on; injured by being thrown into or on; inured by being

thrown against some part of, or object in; injury from moving part of; object falling in or on; object thrown on;

Collision of railway train or road vehicle except motor vehicle, with object set in motion by motor vehicle; motor vehicle by object set in motion by railway train or road vehicle (motor) (non-motor); pedestrian, railway train, or road vehicle (motor) (non-motor) hit by object set in motion by motor vehicle

E819 Motor vehicle traffic accident of unspecified nature

Motor Vehicle Non-traffic Accident (E20-E825)

E820 Non-traffic accident involving motor-driven snow vehicle

Includes: (motor-driven snow vehicle (not on public highway)):

Breakage of part of; fall from; hit by; overturning of; run over or dragged by.

Collision of motor-driven snow vehicle with animal (being ridden) (-drawn vehicle) another off-road motor vehicle, not on public highway; railway train; other object, fixed or movable; injury caused by rough landing of motor-driven snow vehicle.

E821 Non-traffic accident involving other off-road motor vehicle (caveats are the same as above)

E822 Other motor vehicle non-traffic accident involving collision with moving object

Includes: collision, not on public highway, between motor vehicle, except off-road motor vehicle and: animal, non-motor vehicle, other motor vehicle, except off-road motor vehicle, pedestrian, railway train, other moving object

E823 Other motor vehicle non-traffic accident involving collision with stationary object

Includes: collision, not on public highway, between motor vehicle, except off-road motor vehicle, and any object, fixed or movable, but not in motion.

E824 Other motor vehicle non-traffic accident while boarding and alighting

Includes: (while boarding or alighting from motor vehicle, except off-road motor vehicle, not on public highway

E825 Other motor vehicle accident of other and unspecified nature

Includes: (motor vehicle while in motion, not on public highway)

(caveats are the same as in E818)

Source: Annotated International Classification of Disease 9th Revision Clinical Modification Volume 1. 1998.

Appendix D Power Calculations

Number of cases	Control/case Ratio	Relative Risk	Prevalence in Control Group	Power
915	10	1.21	50.0%	0.80
915	10	1.21	40.0%	0.82
915	10	1.23	30.0%	0.82
915	10	1.25	20.0%	0.80
915	10	1.34	10.0%	0.81
915	10	1.46	5.0%	0.82
915	10	1.59	3.0%	0.82
915	10	1.72	2.0%	0.82
915	10	2.02	1.0%	0.82
915	10	2.45	0.5%	0.80

Given the sample size of 915 cases and a control/cases ratio at 10:1, the study has 80% power to detect a relative risk of 1.25 if the prevalence of a risk factor among controls is 20%. If the prevalence rate is 3%, then the relative risk has to be close to 1.6 to be detected at 80% power.

Appendix E Variable Name Index in Alphabetical Order

Variable Name	Disease/Drug Category	ICD-9-CM/ PTC Codes	Diagnoses / Drug Categories	Disease / Drug
ADRENALS	Cortical Steroids	680400	Adrenals	Drug
AGE	Chronological age		Age in year	Demo-graphic
ALCOHOL	Alcohol/drug abuse	303-305	Alcohol/Drug Dependence/Abuse	Disease
		291-292	Alcoholic/Drug Psychosis	
ANTIBIO	Antibiotics	81202	Aminoglycosides	Drug
		81206	Cephalosporins	
		81207	B-Lactam	
		81208	Chloramphenicol	
		81212	Macrolides	
		81216	Penicillins	
		81224	Tetracyclines	
		81228	Misc Antibiotcs	
		82200	Quinolones	
		82400	Sulfonamides	
ANTICOAG	Anticoagulants	201204	Anticoagulants	Drug
ANTICONV	Anticonvulsants	281208	Benzodiazepines	Drug
		281212	Barbiturates	
		281212*	Hydantoins	
		281204	Misc Anticonvulsants	
ANTIDEPR	Other Antidepressants	281604*	Other Antidepressants	Drug
ANTIEMET	Antiemetics	562200	Antiemetics	Drug
ANTIFUNG	Antifungal	81204	Antifungal Antibiotics	Drug
ANTILIPE	Antilipemic	240600	Antilipemic Agents	Drug

Variable Name	Disease/Drug Category	ICD-9-CM/ PTC Codes	Diagnoses / Drug Categories	Disease / Drug
ANTIPARK	Antiparkinsonian Agents	120804 289200 920000*	Antiparkinsonian Agents Sumatriptan Levodopa and Decarboxylase Inhibitor	Drug
ANXIETY	Anxiety	3000	Anxiety State	Disease
BENIGN	Benign Tumor	210-239	Benign Neoplasm	Disease
BENZODIA	Benzodiazepines	282408	Benzodiazepines	Drug
BLADDER	Disorders of Bladder and Urethra	595-596 597-599 788.3 625.6	Disorders of Bladder Disorders of Urethra Incontinence of Urine Stress Incontinence, Female	Disease
BLD_VESS	Blood vessel	440-448 449-459	Diseases of Arteries, Arterioles and Capillaries Diseases of Vein, Lymphatic and Other Vessel	Disease
BLOOD	Diseases of Blood Formation	280-289	Diseases of Blood and Blood-Forming Organs	Disease
BURN_PSN	Burns and Poisons	940-949 960-979 980-989	Burns Poison by Medicinal and Biological Substances Poison by Non-medicinal Sources	Disease
CANCER	Cancer	140-208	Malignant Neoplasm	Disease
CARVASDRG	Cardiac and hypotensives	240400 240800 241200	Cardiac Drugs (Beta-blocker, ACE Inhibitors) Hypotensives Vasodilators	Drug
CATARACT	Cataracts	366	Cataracts	Disease
COPD	Chronic Obstructive	490-496	Chronic Obstructive Pulmonary	Disease

Variable Name	Disease/Drug Category	ICD-9-CM/ PTC Codes	Diagnoses / Drug Categories	Disease / Drug
	Pulmonary Disease		Disease and Allied Conditions	
COR_CONJ	Disorders of Cornea and Conjunctiva	370 371 372	Keratitis Other Disorder of Cornea Disorders of Conjuctiva	Disease
DEMENTIA	Dementia	290 331 3310 797 2941	Senile Organic Psychotic Condition Other Cerebral Degeneration Alzheimer's Disease Senility Dementia in Conditions Classified Elsewhere	Disease
DEPRESS	Depression	296 311 3004 3091	Affective psychosis (major, bipolar, other) Depressive Disorder NEC Neurotic Depression Prolonged Depressive Reaction	Disease
DIABETES	Diabetes Mellitus	250	Diabetes Mellitus (both Type I and Type II)	Disease
DIURETIC	Diuretics	402800 402810	Diuretics Potassium-Sparing Diuretics	Drug
EAR_DIS	Disorders of Ear	380-388	Disorders of Ear and Mastoid Process	Disease
EPILEPSY	Epilepsy	345	Epilepsy	Disease
ESTROGEN	Estrogens	681600	Estrogens	Drug
EYE_DRG	Drugs for Eye	522000 522400 5200**	Miotics Mydriatics Eye, Ear, Nose and Throat Preparations	Drug

Variable Name	Disease/Drug Category	ICD-9-CM/ PTC Codes	Diagnoses / Drug Categories	Disease / Drug
EYELIDS	Disorders of Eyelids	373 374	Inflammation of Eyelids Other Disorders of Eyelids	Disease
GENITOUR	Disorders of Genitourinary System	610-611 614-629 600-608	Disorders of Breast Diseases of Female Genitourinary System Diseases of Male Genitourinary System	Disease
GI_DRG	Digestive Drugs	564000	Gastrointestinal Drugs	Drug
GLAUCOMA	Glaucoma	365	Glaucoma	Disease
HEARING	Hearing Loss	389	Hearing Loss	Disease
HOSPITAL	Hospitalization		At least one hospital admission	General
HYPERTEN	Hypertension	401-405	Hypertensive Diseases	Disease
HYPOGLYC	Other Hypoglycemics	682020 682092*	Sulfonylurea Acarbose	Drug
INFECTIO	Infectious Diseases	001-136	Infectious Diseases	Disease
INJURY	Injury	800-904 910-939 950-959	Fractures, Dislocation, Sprains, Internal Injuries and Open Wound. Superficial Injury, Contusion, Crushing. Injury to Nerves and Complications	Disease
INSULIN	Insulin	682008	Insulin	Drug
ISCHHD	Ischemic Heart Disease	410-414	Ischemic Heart Disease	Disease
JOINT_DIS	Disorders of Joint and Spine	710-719 720-724 2740	Arthropathies and related Disorders Dorsopathies Gouty Arthropathy	Disease

Variable Name	Disease/Drug Category	ICD-9-CM/ PTC Codes	Diagnoses / Drug Categories	Disease / Drug
LOWGI_DIS	Diseases of Lower Digestive Tract	555-569	Non-infectious Enteritis and Colitis	Disease
MALAISE	Malaise and Migraine	7807 05E*** 06E*** 07E*** 346 7840 30781	Malaise and Fatigue Lethargy Fatigue General Malaise Migraine Headache Tension Headache	Disease
NEPHRITI	Disorders of Kidney	580-589 590-594	Nephritis and Nephrosis Other Diseases of Kidney	Disease
NEUR_MOV	Movement Disorders and Stroke	332 333 342, 344, 348, 438	Parkinson's Disease Other Extrapyramidal Diseases Late effect of stroke	Disease
NOSE_DRG	Nose Drug	5200**	Eye, Ear, Nose and Throat Preperations	Drug
NSAIDS	NSAIDS	280804	Non-Steroidal Anti-inflammatory Agents	Drug
NUM_CHP	Multiple medical conditions		Number of chapters diagnosed (3 or less = "0"; 4 or more = "1")	General
NUM_DRG	Multiple drug use		Number of drug categories (2 or less = "0"; 3 or more = "1")	General
OPIOIDS	Opioids	280808 280812* 480800*	Opiate Agonist Opiate Partial Agonist Antitussives (Codeine, Opium Derivatives)	Drug
OSTEOPAT	Disorders of Bone and cartilage	730-739	Osteopathies, Chodropathies, and Acquired Musculoskeletal	Disease

Variable Name	Disease/Drug Category	ICD-9-CM/ PTC Codes	Diagnoses / Drug Categories	Disease / Drug
			Deformities	
OTH_CERE	Other Cerebrovascular Diseases	430-437	Subarachnoid/intracerebral Hemorrhage Transient Cerebral Ischemia Other Cerebrovascular Diseases	Disease
OTH_DIGE	Other Digestive Diseases	530 540-553 570-579	Disease of Esophagus Appendicitis Other Diseases of Digestive System (liver gallbladder pancreas etc.)	Disease
OTH_ELEC	Other Electrolytic	401000 401200 401800	Ammonia detoxicants Replacement Preparation Potassium Removing Resins	Drug
OTH_ENDO	Other Endocrine Glands and Metabolic Disorders	251-259 270-279	Diseases of other Endocrine Glands Metabolic Disorders	Disease
OTH_EYE	Other Ocular Disorders	360 363,364 367 375-379	Disorders of Globe Disorders of Choriod, Iris and Ciliary Body Disorders of Reflections and Accommodation Other Disorders of the Eye	Disease
OTH_PSYC	Other Psychiatric disorders	295 297 298 300 301	Schizophrenic Disorders Paranoid States Other Non-organic Psychosis Neurotic Disorders (exclude 3000, 3004) Personality Disorders	Disease

Variable Name	Disease/Drug Category	ICD-9-CM/ PTC Codes	Diagnoses / Drug Categories	Disease / Drug
OTH_RESP	Other Respiratory Diseases	470-478 500-519	Other Diseases of the Upper Respiratory Tract Pneumoconioses and Other Lung Diseases Due to External Agents	Disease
OTH_SEDA	Other Sedatives	282404 282492	Barbiturates Misc Anxiolytic Sedatives and Hypnotics	Drug
OTHHEART	Other Heart Disease	393-398 415-429	Chronic Rheumatic Heart Disease Disease of the Pulmonary Circulation	Disease
RESP_INF	Acute Respiratory Infections	460-466	Acute Respiratory Infections	Disease
RETINAL	Retinal Disorders	361 362	Retinal Detachment and Defects Other Retinal Disorders	Disease
RHUMATI	Rheumatism	725-729	Rhuematism (muscle tendons other soft tissues)	Disease
RURAL2	Rural/urban residence		Rural/urban residence based on postal codes	Demo-graphic
SEX	Sex		Sex	Demo-graphic
SKIN	Diseases of Skin and Subcutaneous Tissue	680-709	Diseases of Skin and Subcutaneous Tissue	Disease
SLEEP_DIS	Sleep Disturbances	7805 01A*** 3074	Sleep Disturbance Insomnia Sleep Disorder of Non-Organic Origin	Disease
STOMACH	Diseases of Stomach and Duodenum	531-537	Diseases of Stomach and Duodenum	Disease
SYMPTOM	Ill-defined Conditions	780-799	Symptoms, Signs and ill-defined	Disease

Variable Name	Disease/Drug Category	ICD-9-CM/ PTC Codes	Diagnoses / Drug Categories	Disease / Drug
	and Symptoms and Signs		Conditions (except Sleep Disturbance, Malaise and Fatigue)	
SYN-NAR	Syncope/Narcolepsy	7802 7804 12E*** 13E*** 14E*** 347 7803	Syncope and Collapse Dizziness and Giddiness Syncope – unconsciousness Fainting - vaso-vago attack Dizziness – vertigo Narcolepsy Convulsion	Disease
THYROID	Disorder of Thyroid Gland	240-246	Disorder of Thyroid Gland	Disease
TOPANTIF	Topical Antifungal	840408**	Antifungals	Drug
TRICYCLIC	Tricyclic Antidepressants	281604*	Tricyclic Antidepressants	Drug
VIS_DIS	Visual Disturbance	368 369	Visual Disturbance Unspecified Visual Disturbance	Disease

Notes: ICD-9-CM: International Classification of Diseases 9th Edition – Clinical Modification

PTC: Pharmaceutical Therapeutic Classification

* ATC (Anatomical Therapeutic Classification) codes are used to identify the specified drugs.

** DIN (Drug Identification Number) codes are used to identify the specified drugs.

**** Codes specific to Alberta Health Care Billing System (non ICD-9-CM codes)

Appendix F Multivariate Logistic Regression Models

Table F1 Full Model

Categories	Variable Name	Beta Estimates	S.E.	Wald	Sig.	Adjusted OR	95.0% C.I.for Adjusted OR	
							Upper	Lower
Mental, Neurological Disorders and Psychoactive Drugs	DEPRESS	0.20	0.12	2.77	***0.10***	1.22	0.97	1.54
	TRICYCLI	(0.11)	0.19	0.33	0.57	0.90	0.62	1.31
	ANTIDEPR	0.43	0.16	6.93	**0.01**	1.53	1.11	2.10
	ANXIETY	(0.07)	0.13	0.29	0.59	0.93	0.72	1.20
	SLEEP_DIS	0.35	0.16	4.87	**0.03**	1.43	1.04	1.95
	BENZODIA	0.20	0.11	3.16	***0.08***	1.22	0.98	1.52
	OTH_SEDA	(0.26)	0.17	2.42	0.12	0.77	0.56	1.07
	ALCOHOL	0.07	0.32	0.05	0.82	1.08	0.57	2.02
	OTH_PSYC	0.02	0.14	0.01	0.90	1.02	0.78	1.33
	ANTIPSYC	(0.40)	0.39	1.07	0.30	0.67	0.31	1.43
	MALAISE	(0.02)	0.13	0.03	0.87	0.98	0.76	1.26
	EPILEPSY	0.48	0.38	1.59	0.21	1.61	0.77	3.38
	ANTICONV	0.12	0.22	0.32	0.57	1.13	0.74	1.74
	SYN_NARC	0.00	0.15	0.00	0.98	1.00	0.75	1.34
	DEMENTIA	(0.44)	0.31	2.01	0.16	0.64	0.35	1.18
	NEUR_MOV	0.34	0.30	1.26	0.26	1.40	0.78	2.55
	ANTIPARK	(0.88)	0.47	3.50	***0.06***	0.41	0.16	1.04
	OTH_CERE	(0.20)	0.18	1.23	0.27	0.82	0.58	1.16
	ANTIEMET	(0.56)	0.34	2.73	***0.10***	0.57	0.29	1.11
Visual, Hearing Disorders and Drugs for Eye and Ear	GLAUCOMA	(0.32)	0.14	5.19	**0.02**	0.72	0.55	0.96
	CATARACT	0.00	0.09	0.00	0.99	1.00	0.84	1.19
	COR_CONJ	0.16	0.11	2.08	0.15	1.17	0.95	1.44
	RETINAL	0.09	0.12	0.52	0.47	1.09	0.86	1.38
	EYELIDS	(0.00)	0.14	0.00	1.00	1.00	0.77	1.31
	VIS_DIST	0.04	0.17	0.04	0.84	1.04	0.74	1.46
	OTH_EYE	(0.15)	0.13	1.24	0.27	0.86	0.67	1.12
	EYE_DRG	0.18	0.12	2.27	0.13	1.20	0.95	1.53
	HEARING	0.29	0.15	3.57	***0.06***	1.34	0.99	1.81
	EAR_DIS	(0.09)	0.10	0.91	0.34	0.91	0.76	1.10
	EAR_DRG	(0.16)	0.54	0.08	0.77	0.86	0.29	2.48

Categories	Variable Name	Beta Estimates	S.E.	Wald	Sig.	Adjusted OR	95.0% C.I.for Adjusted OR	
Musculoskeletal	JOIN_DIS	0.17	0.08	4.51	**0.03**	1.18	1.01	1.38
Disorders and Pain	*RHEUMATI*	0.02	0.08	0.05	0.81	1.02	0.87	1.20
Relievers	NSAIDS	(0.06)	0.10	0.44	0.51	0.94	0.78	1.13
	OPIOIDS	(0.05)	0.11	0.25	0.62	0.95	0.76	1.17
	OSTEOPAT	(0.14)	0.12	1.25	0.26	0.87	0.68	1.11
Diseases of Endocrine	DIABETES	0.31	0.15	4.49	**0.03**	1.37	1.02	1.83
System and	INSULIN	0.19	0.25	0.56	0.45	1.21	0.74	1.97
Treatments	HYPOGLYC	(0.30)	0.19	2.58	0.11	0.74	0.51	1.07
	THYROID	(0.03)	0.15	0.03	0.85	0.97	0.73	1.30
	OTH_ENDO	(0.09)	0.10	0.83	0.36	0.91	0.75	1.11
	ADRENALS	0.16	0.13	1.58	0.21	1.17	0.91	1.50
	OTH_ELEC	(0.08)	0.19	0.20	0.66	0.92	0.64	1.33
	ESTROGEN	(0.16)	0.15	1.27	0.26	0.85	0.64	1.13
Cardiovascular	ISCHHD	0.08	0.11	0.58	0.44	1.08	0.88	1.34
Disorders and	OTHHEART	(0.02)	0.10	0.03	0.85	0.98	0.80	1.20
Treatments	*ANTICOAG*	0.02	0.17	0.02	0.89	1.02	0.73	1.44
	ANTILIPE	(0.14)	0.14	1.05	0.31	0.87	0.67	1.14
	BLD_VESS	(0.12)	0.11	1.23	0.27	0.89	0.71	1.10
	HYPERTEN	(0.08)	0.09	0.95	0.33	0.92	0.78	1.09
	DIURETIC	0.19	0.10	3.48	***0.06***	1.21	0.99	1.49
	CARVASDRG	(0.28)	0.10	8.66	**0.00**	0.75	0.62	0.91
Respiratory Disorders	RESP_INF	0.22	0.08	7.40	**0.01**	1.24	1.06	1.45
and Treatments	ANTIBIOT	0.08	0.09	0.85	0.36	1.09	0.91	1.29
	ANTIFUNG	(0.33)	0.30	1.23	0.27	0.72	0.40	1.29
	COPD	(0.03)	0.10	0.08	0.78	0.97	0.80	1.19
	OTH_RESP	0.04	0.12	0.09	0.76	1.04	0.82	1.30
Digestive Disorders	STOMACH	0.14	0.11	1.58	0.21	1.15	0.92	1.43
and Treatments	LOWGIDIS	0.24	0.10	5.24	**0.02**	1.27	1.03	1.56
	OTH_DIGE	0.04	0.11	0.14	0.71	1.04	0.84	1.29
	GI_DRG	0.02	0.10	0.05	0.81	1.02	0.84	1.25
Diseases of Urinary	*NEPHRITI*	(0.23)	0.21	1.27	0.26	0.79	0.53	1.19
System	BLADDER	0.04	0.10	0.15	0.69	1.04	0.85	1.28
Diseases of other	INJURY	0.39	0.08	27.25	**0.00**	1.48	1.28	1.72
Systems	BURN_PSN	0.39	0.25	2.52	0.11	1.48	0.91	2.41
	SKIN	0.11	0.08	2.04	0.15	1.12	0.96	1.30
	TOPANTIF	0.58	0.30	3.84	***0.05***	1.79	1.00	3.19

Categories	Variable Name	Beta Estimates	S.E.	Wald	Sig.	Adjusted OR	95.0% C.I.for Adjusted OR	
	CANCER	(0.12)	0.11	1.12	0.29	0.89	0.71	1.11
	BENIGN	(0.07)	0.10	0.50	0.48	0.93	0.76	1.14
	INFECTIO	(0.05)	0.10	0.28	0.60	0.95	0.77	1.16
	BLOOD	0.18	0.14	1.63	0.20	1.19	0.91	1.57
	SYMPTOMS	(0.08)	0.09	0.77	0.38	0.92	0.77	1.10
	GENITOUR	0.06	0.09	0.51	0.48	1.07	0.90	1.27
Demographic Factors	AGE	0.00	0.01	0.32	0.57	1.00	0.99	1.02
	SEX	0.31	0.08	14.25	**0.00**	1.37	1.16	1.61
	RURAL	0.11	0.10	1.16	0.28	1.12	0.91	1.37
General Health Measures	HOSPITAL	(0.06)	0.09	0.41	0.52	0.94	0.79	1.13
	NUM_CHP	0.22	0.12	3.14	***0.08***	1.24	0.98	1.58
	NUM_DRG	0.21	0.11	3.56	***0.06***	1.23	0.99	1.54
	Constant	(3.34)	0.47	50.13	**0.00**	0.04		

Note: 1. Variables in *italic* were removed in the next stage of modeling.

2. Significance levels printed in **bold** are <=.05; ***bold italic*** are between .05 and .10

Table F2 Reduced Model I

Categories	Disease-treatment groups	Variable Names	Beta estimates	S.E.	Wald	Sig.	Adjusted OR	95.0% C.I.for Adjusted OR	
								Lower	Upper
Mental, Neurological Disorders and Psychoactive Drugs	Group 1	DEPRESS	0.19	0.12	2.56	0.11	1.21	0.96	1.52
		TRICYCLI	(0.11)	0.19	0.33	0.57	0.90	0.62	1.30
		ANTIDEPR	0.42	0.16	6.91	0.01	1.53	1.11	2.09
	Group 2	*ANXIETY*	(0.08)	0.13	0.39	0.53	0.92	0.72	1.19
		SLEEP_DIS	0.36	0.16	5.08	0.02	1.43	1.05	1.96
		BENZODIA	0.20	0.11	3.19	0.07	1.22	0.98	1.52
		OTH_SEDA	(0.26)	0.17	2.50	0.11	0.77	0.56	1.06
		ALCOHOL	0.04	0.32	0.02	0.90	1.04	0.56	1.95
	Group 3	*OTH_PSYC*	0.01	0.14	0.01	0.92	1.01	0.78	1.32
		ANTIPSYC	(0.43)	0.39	1.25	0.26	0.65	0.31	1.38
		MALAISE	(0.02)	0.13	0.02	0.89	0.98	0.77	1.26
	Group 4	EPILEPSY	0.48	0.38	1.61	0.21	1.61	0.77	3.38
		ANTICONV	0.09	0.22	0.18	0.67	1.10	0.72	1.68
		SYN_NARC	(0.01)	0.15	0.00	0.97	0.99	0.75	1.32
		DEMENTIA	(0.45)	0.31	2.10	0.15	0.64	0.35	1.17
	Group 5	*NEUR_MOV*	0.35	0.30	1.36	0.24	1.42	0.79	2.57
		ANTIPARK	(0.87)	0.47	3.40	0.07	0.42	0.17	1.06
		OTH_CERE	(0.22)	0.18	1.53	0.22	0.80	0.57	1.14
		ANTIEMET	(0.57)	0.34	2.91	0.09	0.56	0.29	1.09
Visual, Hearing Disorders and Drugs for Eye and Ear	Group 5	GLAUCOMA	(0.33)	0.14	5.30	0.02	0.72	0.55	0.95
		CATARACT	0.01	0.09	0.01	0.94	1.01	0.85	1.20
		COR_CONJ	0.16	0.11	2.13	0.14	1.17	0.95	1.44
		RETINAL	0.08	0.12	0.44	0.50	1.08	0.86	1.37
		EYELIDS	(0.01)	0.14	0.00	0.95	0.99	0.76	1.29
		VIS_DIST	0.05	0.17	0.10	0.75	1.06	0.75	1.48
		OTH_EYE	(0.16)	0.13	1.42	0.23	0.86	0.66	1.11
		EYE_DRG	0.18	0.12	2.15	0.14	1.19	0.94	1.51
		HEARING	0.26	0.15	2.96	0.09	1.30	0.96	1.75
Musculoskeletal Disorders and Pain Relievers	Group 6	JOIN_DIS	0.16	0.08	4.40	0.04	1.18	1.01	1.38
		RHEUMATI	0.01	0.08	0.00	0.95	1.01	0.86	1.18
		NSAIDS	(0.06)	0.10	0.45	0.50	0.94	0.78	1.13

Categories	Disease-treatment groups	Variable Names	Beta estimates	S.E.	Wald	Sig.	Adjusted OR	95.0% C.I.for Adjusted OR	
		OPIOIDS	(0.08)	0.11	0.49	0.48	0.93	0.75	1.15
Diseases of Endocrine System and Treatments	Group 7	DIABETES	0.31	0.15	4.36	0.04	1.36	1.02	1.82
		INSULIN	0.19	0.25	0.55	0.46	1.20	0.74	1.96
		HYPOGLYC	(0.28)	0.19	2.24	0.13	0.75	0.52	1.09
		ADRENALS	0.16	0.13	1.52	0.22	1.17	0.91	1.50
Cardiovascular Disorders and Treatments	Group 8	ISCHHD	0.03	0.10	0.08	0.78	1.03	0.84	1.26
		OTHHEART	(0.04)	0.10	0.17	0.68	0.96	0.79	1.16
		HYPERTEN	(0.08)	0.08	0.95	0.33	0.92	0.78	1.09
		DIURETIC	0.19	0.10	3.38	0.07	1.20	0.99	1.47
		CARVASDRG	(0.28)	0.09	8.62	0.00	0.76	0.63	0.91
Respiratory Disorders and Treatments	Group 9	RESP_INF	0.22	0.08	7.58	0.01	1.24	1.06	1.45
		ANTIBIOT	0.09	0.09	0.98	0.32	1.09	0.92	1.30
		ANTIFUNG	(0.36)	0.30	1.41	0.23	0.70	0.39	1.26
		COPD	(0.02)	0.10	0.02	0.88	0.98	0.81	1.20
Digestive Disorders and Treatments	Group 10	*STOMACH*	0.14	0.11	1.54	0.22	1.15	0.92	1.42
		LOWGIDIS	0.20	0.10	4.02	0.04	1.23	1.00	1.50
		GI_DRG	0.02	0.10	0.06	0.81	1.02	0.84	1.25
Diseases of other Systems		INJURY	0.39	0.08	26.73	0.00	1.48	1.27	1.71
		BURN_PSN	0.39	0.25	2.51	0.11	1.48	0.91	2.40
	Group 11	*SKIN*	0.09	0.08	1.34	0.25	1.09	0.94	1.27
		TOPANTIF	0.56	0.29	3.58	0.06	1.74	0.98	3.10
		BLADDER	0.02	0.10	0.05	0.82	1.02	0.84	1.25
Demographic Factors		AGE	0.00	0.01	0.48	0.49	1.00	0.99	1.02
		SEX	0.34	0.08	19.93	0.00	1.41	1.21	1.64
		RURAL2	0.13	0.10	1.60	0.21	1.14	0.93	1.40
General Health Measures		*HOSPITAL*	(0.08)	0.09	0.70	0.40	0.93	0.78	1.11
		NUM_CHP	0.13	0.11	1.26	0.26	1.13	0.91	1.41
		NUM_DRG	0.17	0.11	2.54	0.11	1.19	0.96	1.47
		Constant	(3.46)	0.46	56.91	0.00	0.03		

Note: 1. Variables in *italic* were removed in the next stage of modeling.

2. Signifieance levels printed in **bold** are <=.05; ***bold italic*** are between .05 and .10

Table F3 Reduced Model II

Variable Names	Beta Estimates	S.E.	Wald	Sig.	Adjusted OR	95.0% C.I.for Adjusted OR	
						Lower	Upper
DEPRESS	0.18	0.12	2.43	0.12	1.20	0.95	1.50
ANTIDEPR	0.41	0.16	6.81	**0.01**	1.51	1.11	2.06
SLEEP_DIS	0.35	0.16	4.82	**0.03**	1.42	1.04	1.93
BENZODIA	0.23	0.11	4.32	**0.04**	1.25	1.01	1.55
OTH_SEDA	(0.23)	0.16	1.91	0.17	0.80	0.58	1.10
GLAUCOMA	(0.32)	0.14	5.09	**0.02**	0.73	0.55	0.96
COR_CONJ	0.16	0.10	2.34	0.13	1.17	0.96	1.44
EYE_DRG	0.24	0.12	4.25	**0.04**	1.27	1.01	1.60
JOIN_DIS	0.20	0.07	7.15	**0.01**	1.22	1.05	1.41
DIABETES	0.32	0.15	4.80	**0.03**	1.38	1.03	1.83
INSULIN	0.18	0.25	0.55	0.46	1.20	0.74	1.95
HYPOGLYC	(0.25)	0.19	1.84	0.17	0.78	0.54	1.12
ISCHHD	0.05	0.10	0.23	0.63	1.05	0.86	1.27
DIURETIC	0.19	0.09	4.11	**0.04**	1.21	1.01	1.46
CARVASDRG	(0.27)	0.08	10.39	**0.00**	0.77	0.65	0.90
RESP_INF	0.26	0.08	12.30	**0.00**	1.30	1.12	1.51
ANTIBIOT	0.15	0.08	3.40	0.07	1.16	0.99	1.36
LOWGIDIS	0.25	0.10	6.21	**0.01**	1.28	1.05	1.55
INJURY	0.42	0.07	33.48	**0.00**	1.52	1.32	1.76
TOPANTIF	0.59	0.29	4.17	**0.04**	1.81	1.02	3.20
AGE	0.00	0.01	0.38	0.54	1.00	0.99	1.02
SEX	0.34	0.08	20.68	**0.00**	1.41	1.21	1.63
RURAL2	0.11	0.10	1.18	0.28	1.12	0.91	1.37
Constant	(3.33)	0.44	56.86	**0.00**	0.04		

Note: Significance levels printed in **bold** are <= .05.

Appendix G Examination of Log Linear Assumption of the Age Variable

1. Determine quartiles of age

Percentile	Age
25	68
50	72
75	76

2. Re-code age into categorical variable with 4 quartile levels

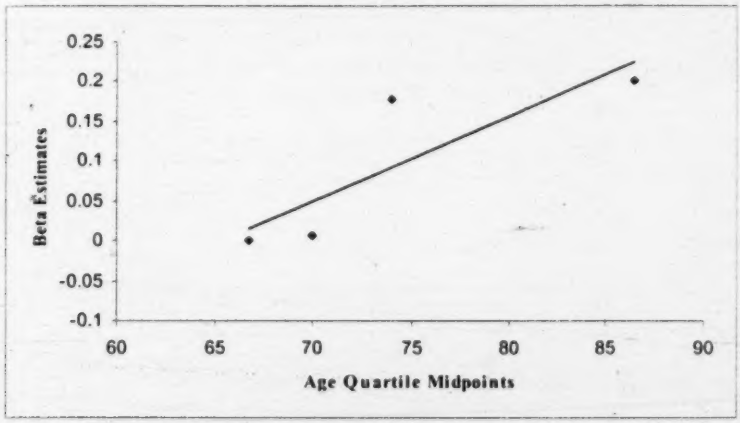
65.5 <= Age < 68 → 0
68 <= Age < 72 → 1
72 <= Age < 76 → 2
76 <= Age <= 97 → 3

3. Fit logistic regression model with new age variable

Variable	B	S.E.	Wald	df	Sig	R	Exp(B)
AGE_CAT			6.0243	3	.1104	.0023	
AGE_CAT(1)	.0059	.1147	.003	1	.9587	.0000	1.0060
AGE_CAT(2)	.1768	.1168	2.29	1	.1301	.0078	1.1933
AGE_CAT(3)	.2008	.1111	3.26	1	.0706	.0163	1.2224
Constant	-2.0486	.0873	550.17	1	.0000		

4. Plot beta against midpoint of quartiles:

5. The log linear assumption is deemed to be met based on above plot.



Appendix H Univariate Regression Models

Categories	Variables	B	S.E.	Wald	Sig.	Crude OR	95.0% C.I.for Crude OR	
							Lower	Upper
Mental, Neurological Disorders and Psychoactive Drugs	**DEPRESS**	0.49	0.10	24.39	**0.00**	1.64	1.35	1.99
	TRICYCLI	0.13	0.18	0.48	0.49	1.13	0.79	1.62
	ANTIDEPR	0.65	0.14	22.54	**0.00**	1.92	1.47	2.52
	ANXIETY	0.21	0.12	3.05	0.08	1.24	0.97	1.57
	SLEEP_DIS	0.63	0.15	18.56	**0.00**	1.89	1.41	2.52
	BENZODIA	0.47	0.10	23.31	**0.00**	1.61	1.33	1.95
	OTH_SEDA	0.14	0.15	0.83	0.36	1.15	0.85	1.55
	ALCOHOL	0.42	0.30	1.95	0.16	1.52	0.84	2.73
	OTH_PSYC	0.32	0.13	6.43	**0.01**	1.38	1.08	1.77
	ANTIPSYC	(0.20)	0.37	0.31	0.58	0.81	0.40	1.68
	MALAISE	0.24	0.12	3.91	**0.05**	1.27	1.00	1.60
	EPILEPSY	0.70	0.35	4.03	**0.04**	2.01	1.02	3.98
	ANTICONV	0.44	0.20	4.93	**0.03**	1.56	1.05	2.30
	SYN_NARC	0.17	0.14	1.57	0.21	1.19	0.91	1.55
	DEMENTIA	(0.09)	0.29	0.09	0.76	0.91	0.52	1.62
	NEUR_MOV	0.17	0.27	0.38	0.54	1.18	0.70	1.99
	ANTIPARK	(0.45)	0.42	1.15	0.28	0.64	0.28	1.46
	OTH_CERE	0.04	0.17	0.05	0.82	1.04	0.75	1.44
	ANTIEMET	(0.35)	0.33	1.12	0.29	0.71	0.37	1.35
Visual and auditory Disorders, and Drugs for Eye and Ear	GLAUCOMA	(0.12)	0.13	0.81	0.37	0.89	0.69	1.15
	CATARACT	0.14	0.08	3.07	0.08	1.15	0.98	1.35
	COR_CONJ	0.34	0.10	11.62	**0.00**	1.40	1.15	1.70
	RETINAL	0.22	0.11	3.92	**0.05**	1.25	1.00	1.55
	EYELIDS	0.21	0.13	2.74	0.10	1.23	0.96	1.58
	VIS_DIST	0.14	0.17	0.69	0.41	1.15	0.83	1.59
	OTH_EYE	0.03	0.13	0.04	0.84	1.03	0.80	1.31
	EYE_DRG	0.29	0.10	7.85	**0.01**	1.34	1.09	1.65
	HEARING	0.44	0.15	8.84	**0.00**	1.55	1.16	2.06
Musculoskeletal Disorders and Pain Relievers	**JOIN_DIS**	0.40	0.07	32.80	**0.00**	1.49	1.30	1.71

Categories	Variables	B	S.E.	Wald	Sig.	Crude OR	95.0% C.I.for Crude OR	
	RHEUMATI	0.24	0.08	10.06	**0.00**	1.27	1.10	1.47
	NSAIDS	0.18	0.09	4.17	**0.04**	1.19	1.01	1.41
	OPIOIDS	0.27	0.10	7.29	**0.01**	1.31	1.08	1.58
Diseases of Endocrine System and Treatments	**DIABETES**	0.35	0.10	12.11	**0.00**	1.42	1.17	1.74
	INSULIN	0.50	0.22	5.27	**0.02**	1.65	1.08	2.54
	HYPOGLYC	0.14	0.14	0.96	0.33	1.15	0.87	1.51
	ADRENALS	0.41	0.11	13.37	**0.00**	1.50	1.21	1.87
Cardiovascular Disorders and Treatments	**ISCHHD**	0.20	0.09	5.08	**0.02**	1.23	1.03	1.47
	OTHHEART	0.18	0.09	4.31	**0.04**	1.20	1.01	1.42
	HYPERTEN	(0.02)	0.07	0.06	0.81	0.98	0.85	1.13
	DIURETIC	0.20	0.09	5.32	**0.02**	1.22	1.03	1.44
	CARVASDRG	(0.04)	0.07	0.33	0.57	0.96	0.83	1.10
Respiratory Disorders and Treatments	**RESP_INF**	0.44	0.07	40.28	**0.00**	1.56	1.36	1.78
	ANTIBIOT	0.37	0.08	24.86	**0.00**	1.45	1.26	1.69
	ANTIFUNG	(0.06)	0.29	0.04	0.84	0.94	0.53	1.67
	COPD	0.31	0.09	12.15	**0.00**	1.36	1.15	1.63
Digestive Disorders and Treatments	***GI_DRG***	0.35	0.09	16.24	**0.00**	1.41	1.20	1.67
	LOWGIDIS	0.49	0.09	26.68	**0.00**	1.63	1.35	1.96
	STOMACH	0.43	0.10	18.76	**0.00**	1.53	1.26	1.86
Diseases of other Systems	**INJURY**	0.56	0.07	65.60	**0.00**	1.76	1.53	2.01
	BURN_PSN	0.64	0.24	7.48	**0.01**	1.90	1.20	3.01
	SKIN	0.32	0.07	20.53	**0.00**	1.37	1.20	1.58
	TOPANTIF	0.73	0.29	6.51	**0.01**	2.07	1.18	3.63
	BLOOD	0.46	0.13	12.11	**0.00**	1.58	1.22	2.05
Demographic Factors	AGE	0.01	0.01	2.72	0.10	1.01	1.00	1.02
	SEX	0.24	0.07	10.85	**0.00**	1.27	1.10	1.46
	RURAL2	0.11	0.10	1.10	0.29	1.11	0.91	1.35
General health measures	***HOSPITAL***	0.29	0.08	8.64	**.003**	1.26	1.08	1.46
	NUM_CHP	0.59	0.09	45.7	**0.00**	1.81	1.52	2.15
	NUM_DRG	0.40	0.07	32.3	**0.00**	1.48	1.30	1.70

Note: 1. Significance levels printed in **bold** are <= .05.

2. Variables in **bold** were statistically significant in both univariate and multivariate models.
3. Variables in ***bold italic*** were statistically significant in univariate models but later removed due to insignificant contribution to multivariate models.
4. See Appendix E for complete index on variable names.